

UNITED STATES DISTRICT COURT  
FOR THE  
DISTRICT OF MASSACHUSETTS

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JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY, and MANULIFE INSURANCE  
COMPANY (f/k/a INVESTORS  
PARTNER LIFE INSURANCE  
COMPANY),

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

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CIVIL ACTION NO. 05-11150-DPW

**AFFIDAVIT OF STEPHEN J. BLEWITT**

**CONTINUATION OF EXHIBITS**

**PLs' DJ**

November 2000  
ABT-594 Project Status Report

**Monthly Highlights**

- In-life phase of 2-year mouse carcinogenicity studies completed mid-November
- Proposals and timelines from 3 patient recruitment firms were reviewed, with a conclusion reached that hiring a recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.
- USAN approval for the generic / chemical name for ABT-594 was received. The United States Adopted Name for ABT-594 (A-166594.47) is ebanidine tosylate (ē-ba-ni-klēn to-se-lāt.)
- Preliminary commercial capsule design selected by AI and PPD Marketing, with input from across the project team. The primary parameters are: Size 3 hard gelatin capsules, 2 strengths / colors: 75 mcg - 1/2 light yellow, 1/2 white, 150 mcg - both halves light yellow, printed with strength and trade name (TBD.)

Key Progress Gauges - November Accomplishments	Target Date	Status
• Final decision on commercial capsule parameters to be provided by NPD to PARD	11/10	Complete - All information provided by 11/13.
• Achieve enrollment of at least 220 patients in M99-114 by 11/30	11/30	Complete - 246 patients enrolled as of 11/30
• Complete 7 "good will" site visits for M99-114	11/30	Complete

December Projections	Target Date	Status
• Portfolio analysis team review of forecast and expense projections	12/19	
• Achieve enrollment of at least 260 patients in M99-114 by 12/31	12/31	

1 of 6

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November 2000  
ABT-594 Project Status Report

*Key Issues/Decisions/Events*

Area	Issue/Decision/Event	Progress
Venture	Extension of enrollment for Phase IIb Neuropathic Pain through 03/01	Enrollment is going better than projected during the November / December Holiday season, where we had anticipated a slow-down. Impact on timeline will be reviewed in January.
PARD	During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules.	This issue has been reviewed with PARD, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made. SPD to deliver approx. 2 grams of the purified F' material mid-December for further testing and confirmation.
SPD	Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.	PARD Analytical is completing analysis of lab-scale batch and intermediates to assure there are no new impurities to be found. Plans are to manufacture a single production-scale lot in early-2001 with available raw materials, and to wait on the second and third NDA lots until after the Go / No Go decision.
NPD	Portfolio analysis process is underway for ABT 594 and will impact budget allocation for 2001. A new forecast using updated NPD forecast model with clearly defined product profile and high and low case estimates is being developed and will be reviewed by core team prior to final conduct of portfolio prioritization.	ABT 594 portfolio team will review the forecasts and profile on 12/19/00. Final adjustments, if any, will need to be submitted no later than 1/15/01 (just prior to prioritization meeting).
Toxicology	6-month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long-term toxicology studies.	No adenomas have been found in the study. The in-life phase of the 2-year carcinogenicity study is complete and preliminary data on tumor findings should be available 1Q2001.

2 of 6

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November 2000  
ABT-594 Project Status Report

Project Cost Summary - October						
\$000's Activity	Cumulative through 1999	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	22.9	7.0	7.6	7.9	.3	157.1
CMC (PARD & SPD)	13.0	3.0	3.2	2.6	-.6	27.6
Drug Safety	8.7	2.8	3.0	2.4	-.6	18.3
Other Support Costs	0.7	.5	.6	1.5	.9	12.2
Total	50.5	13.3	14.4	14.4	0.0	215.2

File NDA = 9/2003

Clinical Study Progress					
Protocol # - Study Name	Start (1 <sup>st</sup> Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients	Current Enrollment
M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,000	320	246 (as of 11/30)

3 of 6

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**November 2000**  
**ABT-594 Project Status Report**

**Business Rationale**

Date: October 2000  
 Franchise: Neuroscience  
 Venture: Analgesia

ABT #: ABT-594  
 Trade & Generic Name: TBD, ebanicline tosylate  
 Mechanism of Action: Neuronal Nicotinic Receptor (NMR) Agonist

Indications: Neuropathic Pain  
 Chronic Pain (publication only)

Product Profile				
Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Not scheduled	12/1996	High	1Q04	High
Chronic nociceptive pain efficacy	10/1999	Medium	2Q01	High
Neuropathic pain claim	6/1999	Medium	2Q01	High
General pain claim	12/1996	N/A	N/A	High
Moderate to moderately severe pain				
No tolerance/dependence or withdrawal	9/1998	Medium	1Q03	High
Very few abnormal LFTs	9/1998	High	2Q01	High
Low nausea/vomiting at effective dose	8/1999	Medium	2Q01	High
Other safety OK	9/1998	Medium	2Q01/1Q03	High
No differential efficacy (nicotine users vs. non users)	9/1998	High	2Q01/1Q03	High
No differential side effect profile (nicotine users vs. non users)	9/1998	Medium	2Q01/1Q03	Medium
No reinitiation of cravings in ex-nicotine users	9/1998	N/A	N/A	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	Low	4Q01	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	N/A	N/A	Medium
BID dosing	6/1999	High	2Q01	High
No major drug interactions	12/1996	High	1Q03	Medium
Titration of 2-5 days duration is required to minimize nausea and vomiting at effective dose.	9/1999	Medium	1Q00	High

\* Probability Key:  
 High = 70-100%  
 Medium = 30-69%  
 Low = 0-29%

Market Forecast			
	PPC/DDC 12/1996*	Plan as of 6/1998*	Current Revised 10/2000**
Patent Status:	10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
NDA Filing:	12/1999 (acute) 6/2001 (chronic)	12/2001	9/2003
Ex-U.S. Filings:	Same as above - Eur N/A - Jpn	12/2001 - Eur 12/2003 - Jpn	9/2003
Projected U.S. Launch:	12/2001 (acute) 12/2002 (chronic)	6/2003	9/2004
Projected ex-U.S. Launches:	Same as above - Eur N/A - Jpn	12/2003 - Eur 9/20/2004 - Jpn	Q2 2005 ("average" launch for EU, LA, Canada) Q4 2005 (Average launch for Japan, PAA)
Peak TRx Share, U.S.:	6.6% (patients)	5% (Rx)	20% (Neuropathic pain) 10% (Persistent Chronic Pain)
Peak TRx Share, ex-U.S.:	5.4% (patients)	5% (patients)	same as US assumptions
Peak Sales, U.S.: (SMM)	\$265	\$618	\$367
Peak Sales, ex-U.S.: (SMM)	\$308	\$310	\$466
Pre-Tax NPV @ 15%, ex-U.S.: (SMM)	\$338	\$305	\$359
After-Tax NPV @ 12.5%, U.S.: (SMM)	\$412	\$813	\$296
Avg. daily dose	50 mg	200 mcg	150 mcg
Target Drug Cost/Kg at Launch	\$2,500	\$2,500	\$40,000 (base eq.)
SMM at Launch	94.8%	97.2%	98.6%
SMM at Year 5			

\* Forecast based on general pain target indication

\*\* Forecast based on neuropathic pain indication and published study in chronic pain

4 of 6

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**November 2000  
ABT-594 Project Status Report**

**Project Overview**

Metrics Dates	
Description	Date
DDC Meeting	12/1996 (PPCC)
Start of first GLP animal tox study	2/1997
First dose in human (beg. Phase I)	7/1997
First dose in patient (beg. Phase II)	7/1998
First dose in Phase III	2/2002 (est.)
Last Patient/Last Visit	4/2003 (est.)
NDA Filing	9/2003 (est.)
NDA Approval	9/2004 (est.)
Europe (EMEA) Filing	9/2003 (est.)
Europe (EMEA) Approval	TBD
Japan Filing	4/2004 (est.)
Japan Approval	TBD

SPD				
Drug Substance Source/Lot #	KG	Plan 6/1999	Actual Date	Plan 6/1999 Projected Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	On Test	\$ 29,700

\* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

PARD			
Activity	Plan 6/1999	Current Revised 10/00	Actual
Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)	10/1998	10/1998	10/1998
Phase IIb / Formulation (HGC) for Bio Study	3/1999	3/1999	3/1999
Phase III Clinical Supplies Manufactured	9/1999	9/2001	TBD
NDA Lots (3) Completed	6/2000	5/2002	TBD
Completion of 1 Year Stability for NDA	7/2001	7/2003	TBD
Formulation Peer Review	10/2001	TBD	TBD

\* Performed by IDC

Toxicology			
Toxicology Activity	Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology	2/1997	8/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	--	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing

5 of 6

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November 2000  
ABT-594 Project Status Report

*Clinical Study Progress*

Protocol:	M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy
Objective:	The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.
ABT-594 Doses:	150 µg, 225 µg, and 300 µg twice daily (BID)
Comparator Doses:	Placebo
Target Enrollment:	320
Target Cost:	\$3 MM
Actual Cost:	TBD
Status:	Ongoing - 246 patients randomized as of 11/30
Major Findings:	TBD

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6 of 6

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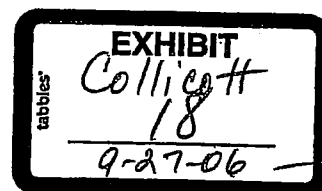
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**ABT-594**

**Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**



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**ABT-594 Opportunity Overview**

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release). Peak sales of ABT-594 are projected to reach over \$420MM in the US and \$362MM ex-US by 2008.

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth. Of even greater impact on total market sales, most of the agents used to treat this population, with this exception of Neurontin, are low-cost, generic products.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

**Market Size / Prevalence**

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.



**Competition, Current Marketed Products:**

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
<b>TOTAL</b>	<b>12.5</b>	<b>5.6%</b>	<b>N/A</b>	<b>N/A</b>
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
<b>TOTAL</b>	<b>\$351</b>	<b>21.7%</b>	<b>\$140</b>	<b>10.1%</b>
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

**Competition, Products in Development**

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through $\alpha 2$ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor, active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

Analgesia Development Pipeline -- Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

### Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events.  Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimoclomol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

**Product / Development Background****Scientific Rationale for ABT-594**

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

**Clinical Studies**

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients are anticipated to be included in the study.

### **Patent Status**

A notice of allowance has been obtained from the United States Patent and Trademark Office on an application providing composition of matter coverage for a large class of structurally related neuronal nicotinic receptor analogs, which encompasses ABT-594 (5246.U.S.) The original filing date for this application dates back to October 9, 1992. The expiration of patent coverage for composition of matter for ABT-594 under this patent is June 2016.

An additional application (6013.US.01) which includes a use claim for ABT-594 species in analgesia was filed in September 1997, with subsequent divisional filing of ABT-594 species composition of matter. Despite this later composition of matter filing for the species claim, it is likely that a "terminal disclaimer" will be necessary that dates the composition of matter claim back to the original genus patent (5246.U.S.) We have paid the issue fee for this patent on July 19, 2000, and are anticipating the patent to issue 90 - 120 days from that date. If this patent is allowed, it will provide 20 years from date of filing for the use of ABT-594 in analgesia, which will extend the patent life of ABT-594 to September 2017.

The original application providing generic composition of matter coverage was filed broadly ex-U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

As additional information regarding potential uses for ABT 594 is gathered, applications to expand the scope of ABT 594's patent will be submitted. A task force consisting of members of NUDDR, the Analgesia Venture, New Product Development, the Neuroscience Franchise, and the Abbott Patent Department will conduct periodic review of the patent.

### **Considerations**

#### **Target Profile:**

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug Interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

*Label Strategy:*

BASE: Indicated for the treatment of diabetic neuropathic pain.

- UPSIDE:
- 1) Treatment of pain associated with OA
  - 2) Treatment of post-herpetic neuralgia
  - 3) Treatment of neuropathic pain
  - 4) Treatment of chronic pain
  - 5) Treatment of cancer pain

*Cost of Goods Sold:*

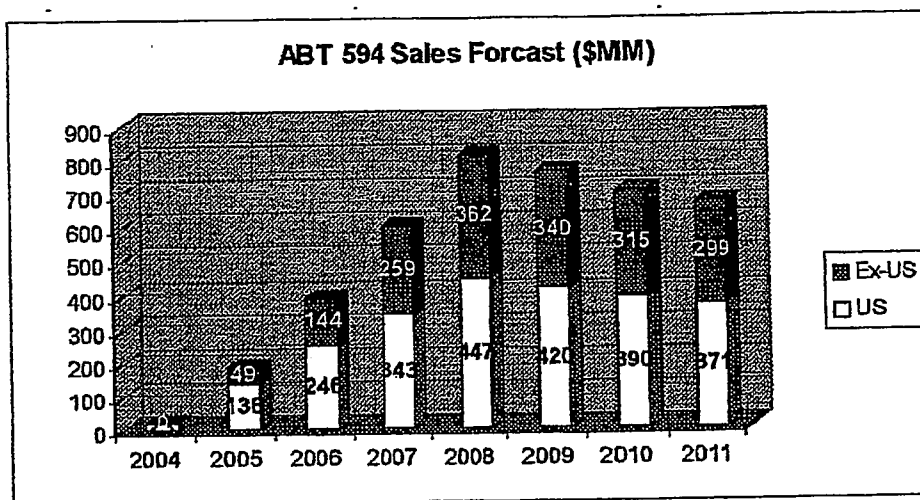
The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

*Pricing:*

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.



**Financial Projections****Key US forecast assumptions:**

- First neuronal nicotinic receptor compound for pain to market
- Indicated for treatment of neuropathic pain; significant publication, or indication, from large scale trial on use in some form of chronic persistent nociceptive pain (e.g., OA) in 2006
- Efficacy greater than gabapentin in neuropathic pain and COX-2s in chronic nociceptive pain
- Good safety profile (no significant warnings or contraindications)
- Tolerability profile in line with other chronic pain products (CNS side effects improved over Neurontin and GI side effects improved over tramadol)
- No addictive potential
- Titration of 3-5 days
- Peak share 20% in neuropathic pain, 10% in chronic, persistent nociceptive pain (including off-label, 'spillover' prescriptions)
- Significant promotional and PR spend in early years
- Physician targets: D6-10 Neurologists, D3-10 Rheumatologists/Endocrinologists, D9-10 PCPs
- Sampling at 80% of details at launch, 5 units per detail, 7 days of therapy per unit
- Cost comparable to Neurontin and Celebrex
- Significant payor discounting
- Stocking at 8% of first year's sales
- Patent expires 12/2016

**Additional Ex-US forecast assumptions:**

- Same profile and peak share assumptions as U.S. forecast
- Price (ASP) = \$0.90 per day, or \$27 per 30 day Rx (comparable to COX-2 pricing)
- Average AI launch assumption is Q1 2005 to allow for additional regulatory filings (COFS and national filings in PAA and LA) and/or pricing negotiations (most markets in Europe) required in AI markets

**PLs' DM**





James  
Sullivan /LAKE/PPRD/ABBO  
TT  
11/02/2000 04:04 PM

To Robert J Weiland/LAKE/PPD/ABBOTT@ABBOTT  
Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT,  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Mike  
Williams/LAKE/PPRD/ABBOTT@ABBOTT, Andrea  
cc Landsberg/LAKE/PPD/ABBOTT@ABBOTT, Larry L  
Lin/LAKE/PPD/ABBOTT@ABBOTT, Rosemarie K  
Waleska/LAKE/PPD/ABBOTT@ABBOTT

bcc

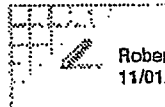
Subject Re: Pharmacia meeting [B]

Bob,

I do not want to make things confusing but I was under the strong impression after the meeting with Dan and John a couple of weeks ago that we were to limit the discussion to ABT-594 only at this time and no discussion of other compounds advanced to clinical status or the preclinical project in general was to be revealed. Dan re-iterated to this to me on his way out of the meeting. Hence, I would suggest that the agenda etc should be limited to

- Preclinical profile of ABT-594 (15-20mins)
- Clinical Profile of ABT-594 (Bulk of time)
- Brief description of the type of collaboration we have in mind.

Thanks  
Jim  
Robert J Weiland



Robert J Weiland  
11/01/2000 16:15

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT  
cc: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Mike Williams/LAKE/PPRD/ABBOTT@ABBOTT,  
Andrea Landsberg/LAKE/PPD/ABBOTT@ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT,  
Larry L Lin/LAKE/PPD/ABBOTT@ABBOTT, Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT  
Subject: Re: Pharmacia meeting [B]

Bruce:

Thank you for your message. Unfortunately with everyone's travel calendar, a pre-planning meeting has not been very feasible.

The primary purpose for this meeting is to share data with Pharmacia that might encourage them to partner with us on this project. Although time has elapsed, Steve A. is aware of this from his days at Abbott, although he may not be fully facile with the most recent data.

At the end of the day, there is no other way I am aware of to broach a partnership without disclosure of the technical and scientific information. Hence, unless there is something particular that we should hold back in this first round, then we need to provide the info. One area where I have a concern is the nausea and vomiting issue. If anyone has a suggestion on how we can handle that without frightening our partner, it would be very well received.

In terms of the meeting, we should be prepared to share with them

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ABBT0120836

- I - Discussion of the existing data / program
- II - Plans for moving the project ahead
- III - Other compounds that have been moved ahead
- IV - Brief description of the type of collaboration we have in mind

The first three should be handled by the Technical Team. The latter by Larry Lin. I apologize, in advance, that I will be out of the country and unable to attend next Tuesday.

Should you have ideas for a better agenda. Please get back to me quickly as I would like to finalize with Dick Welter at Pharmacia.

Best Regards,

Bob

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ABBT0120837

**PLs' DT**

Elizabeth  
Kowaluk/LAKE/PPRD/ABBOTT  
TT  
11/30/2000 05:08 PM

To: Bryan F Cox/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
bcc:  
Subject: Re: 12/6 meeting ☐

Interesting - I wonder that is based on?

Liz

Bryan F Cox

Bryan F Cox  
11/30/2000 05:05 PM

To: Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: 12/6 meeting ☐

Wouldn't miss it for the world. Sadly though, our die may be cast. At SAC today, Jeff Leiden put up a slide today listing ABT-822 as Commercial Viability Questionable.

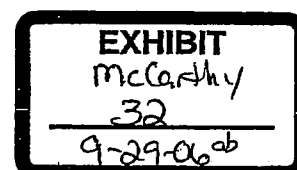
Of course, ABT-594 was painted with the same brush.

Bryan

Silber DEP. EX. NO. 33  
FOR ID., AS OF 2-9-07 BC

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ABBT326427



**PLs' DV**



Marilyn J  
Collicott /LAKE/PPRD/ABBO  
TT

12/06/2000 02:04 PM

To: Michael K Biamesen/LAKE/PPRD/ABBOTT

cc

bcc

Subject: Re: November Monthly Project Status Report, ABT-594 [ ]

Wellllllllllllllllll - OK. I just have a feeling the bottom is going to drop out of this thing in the next few weeks and we'll be lucky to randomize 1-2/week. (Oh God - I'm turning into an Eeyore!!)  
Michael K Biamesen

Michael K Biamesen

12/06/2000 01:07 PM

To: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: November Monthly Project Status Report, ABT-594 [ ]

How about 260 for the randomization goal? We already have 251 !!!!!.  
Marilyn J Collicott



Marilyn J Collicott

12/04/2000 02:13 PM

To: Michael K Biamesen/LAKE/PPRD/ABBOTT  
cc:  
Subject: Re: November Monthly Project Status Report, ABT-594 [ ]

Mike

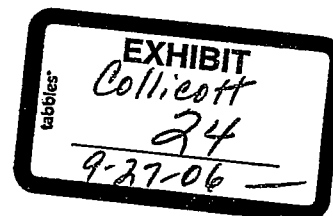
Monthly Highlights:

Reviewed proposals and timelines from 3 subject recruitment firms. Determined that hiring a subject recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.

December Projections:

254 subjects randomized for study M99-114.

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ABBT242373

Draft

Name: Christopher Blum, M.D.  
 Title: Head, Research & Venture

**DIVISION INCENTIVE PLAN GOALS**  
 2001 DIP

Manager: John Leonard

Any approved division incentive plan "DIP" award will be dependent upon division results and individual performance against impact goals and leadership competencies as evaluated by the senior vice president ("Division"). Each impact goal category must have a minimum of one (1) goal and no more than eight (8) goals across all three (3) categories. Impact goal weight minimum is 5%.

	Weighting %	Competency Performance
<b>Leadership Competencies</b> 1. Set Vision and Strategy 2. Build Organization and Inspire People 3. Know the Business 4. Drive Results 5. Make Difficult Decisions 6. Encourage an Open Environment and Knowledge Sharing	20	

Impact Goal Categories	Goal and Expected Result	Results Achieved	Weighting %	Goal Performance
Financial	1. Operate within Plan Head Count of XX and Expenses of \$XXXX, or as modified in Updates or Blue Prints (2000 = XXXX).	1.	15	
Business Process	2. Execute sufficient data for ABT-594 GO/NO GO decision by 2Q 01. • Last patient enrolled in Phase 2 Neuropathic Pain Study 3/01.	2.	15	
	3. IF GO decision for ABT-594, complete preparation for 1Q 02 initiation of Phase 3. • Manufacture bulk drug substance by 3Q 01 to support Phase 3 clinical supplies. • Manufacture clinical supplies by 4Q 01 to support initiation of Phase 3. • End of Phase 2 (or extended) meetings with regulatory authorities by 12/01. • Protocol approval for all planned pivotal studies by 1Q 02.	3.	10	
	4. Achieve ABT-089 transition team GO/NO GO decision by 4Q 01. • Initiate first-in-man study by 4Q 01.	4.	15	
	5. Complete dosage form assessment (sustained-release formulation) by 11/01. • Working with Neuroscience Franchise team, in-license one compound and recommend strategy for company acquisition or alliance by 12/01.	5.	10	
	6. Develop and execute transition team strategy by 2Q 01.	6.	5	
	7. Achieve priority people initiatives. • Ensure Performance Excellence program initiatives are met by year end. 8. Retain 80% of the "O" performers and identified high potentials.	7.	5	
People Management		8.	5	
TOTAL GOAL PERFORMANCE			100	

12/01/00

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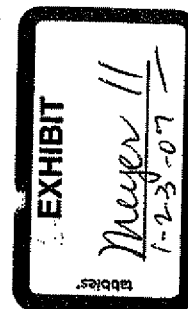
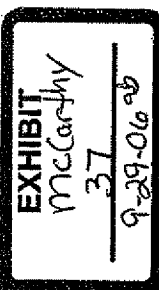
**PLs' EL**



Project Review  
ABT-089 and ABT-594  
February 2, 2001

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ABBT 0002314



## Project Review

- ABT-089

REDACTED

- ABT-594

- Overview, upcoming milestone: June 2001
- Follow-on strategy

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ABBT 0002315

## Neuronal Nicotinic Receptor (NNR) Program

- Scientific leadership position for Abbott
- An emerging diversity of receptors
- Multiple potential therapeutic targets

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ABBT 0002316

ABT-089

REDACTED

HIGHLY  
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ABBT 0002317

ABT-089

REDACTED

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ABBT 0002318

## ABT-594

### *Overview*

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

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ABBT 0002319



**ABT-594**

*Therapeutic Utility*

**Neuropathic Pain**

**Chronic Pain**

**Cancer Pain**

**Diabetic  
Neuropathy**

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ABBT 0002324



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ABBT 0002358

# ABT-594 Project Review February 2, 2001

## Introduction

Chris Siber

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ABBT 0002359

# ABT-594 Project Review

## *Agenda*

- |                           |                  |
|---------------------------|------------------|
| • Introduction            | Chris Silber     |
| • Pharmacological Profile | Jim Sullivan     |
| • Clinical Overview       | Bruce McCarthy   |
| • Commercial Assessment   | Andrea Landsberg |
| • Go/No Go Process        | Bruce McCarthy   |
| • Follow-On Strategy      | Mike Meyer       |

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ABBT 0002360

## ABT-594

### *Overview*

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

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ABBT 0002361



## Pain Prevalence

- 22% primary care patients worldwide have persistent pain
- Neuropathic pain
  - 20% of diabetics
  - 40% of HIV infected
  - 36% of cancer patients

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ABBT 0002362

## Pain Therapeutics Market

- \$12 billion in sales of key classes (NSAIDs, COX-2s, opioids, non-opioids)
- \$700 million in sales of key neuropathic pain compounds
  - use largely off-label
  - low cost generics

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## Neuropathic Pain

### *Treatment*

#### No efficacy

Some efficacy  
(at best 40% vs. 20% placebo)

- Tricyclic antidepressants
    - Amitriptyline, desipramine, etc.
  - Anti-epileptic drugs
    - Carbamazepine
    - Gabapentin (Pregabalin)
    - Topiramate, others
  - Sodium channel blockers
    - Lidocaine
  - Opioids
    - Tramadol
- SSRIs
  - NSAIDs/COX-2

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**Broad-Spectrum, Non-Opioid Analgesic Activity  
by Selective Modulation of Neuronal Nicotinic  
Acetylcholine Receptors**

A.W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon,  
D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz,  
A. H. Dickenson, R. D. Porcett, M. Williams, S. P. Arneric

SCIENCE • VOL. 279 • 2 JANUARY 1998

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ABBT 0002366



## Development Strategy

### Chronic Nociceptive

Osteoarthritis  
Chronic back pain  
Rheumatoid arthritis  
Cancer pain  
Fibromyalgia  
Sickle cell disease  
TMJ disorder  
Bursitis  
Tendinitis  
Chronic visceral pain

### Neuropathic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug-induced polyneuropathy  
HIV predominantly sensory  
neuropathy  
Back pain  
Cancer pain  
Trigeminal neuralgia  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
Complex regional pain  
syndromes (I, II)  
Atypical facial pain  
Phantom limb pain

### Acute

Post-dental surgery  
Sprains and strains  
Acute back pain  
Trauma  
Post-general surgery  
Post-orthopedic  
surgery  
Dysmenorrhea  
Renal colic  
Biliary colic  
Pancreatitis  
Infections

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ABBT 0002366

# Development Strategy

*Choose Portals of Entry*

Molar

Extraction

Acute Pain



Peripheral

Neuropathy

Neuropathic Pain



Osteoarthritis

Chronic Nociceptive

Pain



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ABBT 0002367

# ABT-594

## *Current Label Target*

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

### Upside Claim

- Neuropathic Pain
- Post herpetic neuralgia
- OA Pain
- Chronic Pain
- Cancer Pain

### General Pain Claim

- Not viable due to 1.5 hour onset

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ABBT 0002368

## ABT-594

### *Go/No Go Process*

◦ Decision analysis (DSG) will be used as a tool to determine milestone criteria

- Efficacy and safety
- Titration effects
- Dose selection
- Indications
- Market research

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ABBT 0002369



# ABT-594

## Phase III Clinical Plan

	U.S.	Europe	Japan
Diabetic neuropathy	2 (n=1200)	2 (n=1200)	1 (n=300)
Long-term safety	1 (n=500)	1 (n=500)	-
Gabapentin comparator	-	1 (n=320)	-
Other neuropathic pain (Phase 3B) post herpetic neuralgia, sciatica	2 (n=600)	-	-
Cost (\$ million)	01 6.1	02 59.6	03 55.7
			Total 121.4

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ABBT 0002370

## ABT-594

### *Phase 2 to 3 Transition*

Milestone review

6/01

End of Phase 2 package/request

9/01

Start manufacture Phase 3 supplies

9/01

Ship first Phase 3 supplies

2/02

Initiate Phase 3

3/02

Regulatory filings

9/03

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ABBT 0002371

## ABT-594

### *Overview*

- First-in-class
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- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

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ABBT 0002372

**ABT-594 Project Review  
February 2, 2001  
Pharmacological Profile**

**Jim Sullivan**

**HIGHLY  
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**ABBT 0002373**



## ABT-594: Preclinical Pharmacology

- Rationale for NNRs and pain
  - Knockout, antisense and pharmacological validation
- *in vitro* and *in vivo* profile of ABT-594
  - Efficacy
  - Safety

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ABBT 0002374

# NNRs and Pain: NNRs are Expressed in Pain Pathways

## • CNS

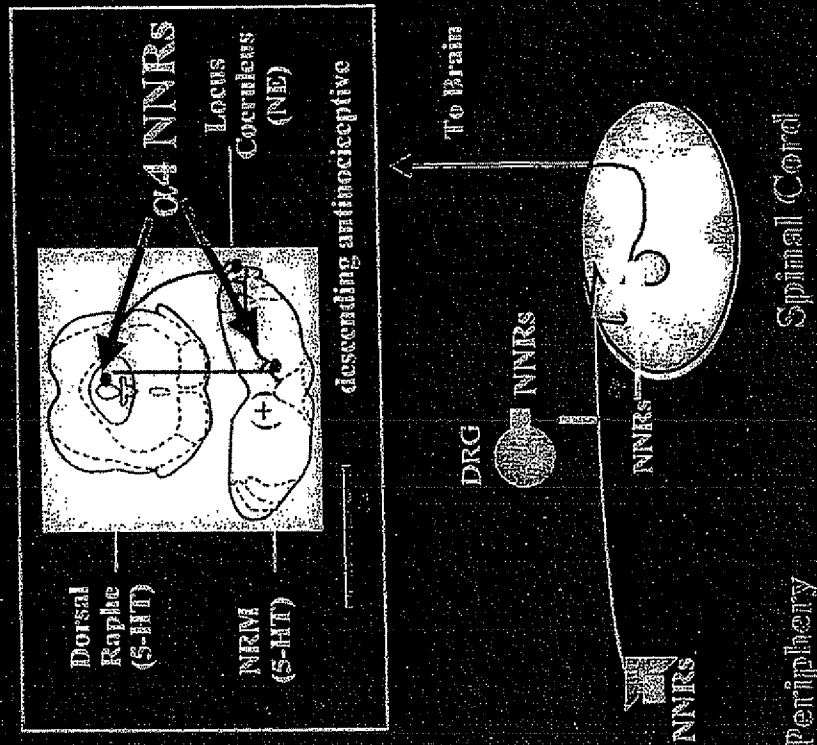
- $\alpha 4$  NNRs are localized in NRM and dorsal raphe (Key CNS pain center)

## • Spinal Cord

- NNRs are expressed in dorsal horn neurons (key spinal cord pain processing center)

## • Sensory Neurons

- $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 7$  NNRs are expressed in DRG and on central and peripheral C-fiber nociceptors

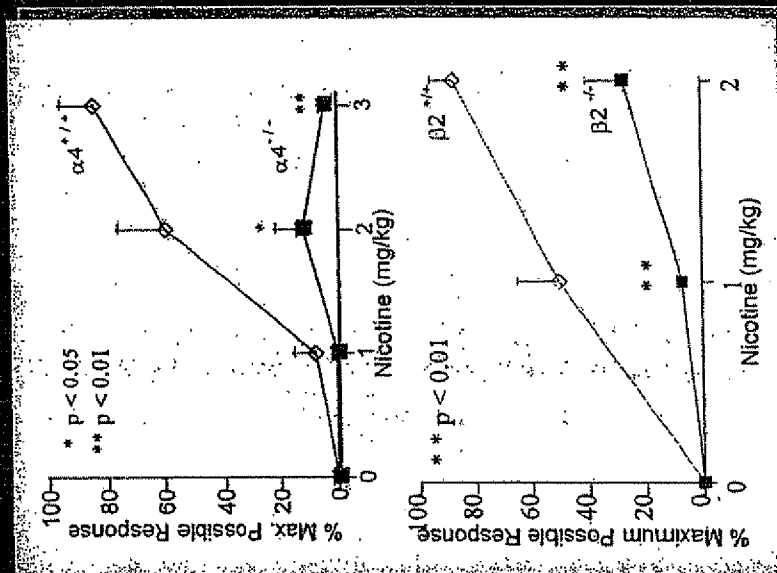


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ABBT 0002375

# NNRs for Pain: Role of $\alpha 4$ and $\beta 2$ NNRS Established Using Knockout Mice

In either  $\alpha 4^{-/-}$  or  $\beta 2^{-/-}$  mice, neither nicotine nor epibatidine was active in the hot plate assay (supraspinal mechanism)



Marubio, et al. *Nature* 1999 398, 805-810.

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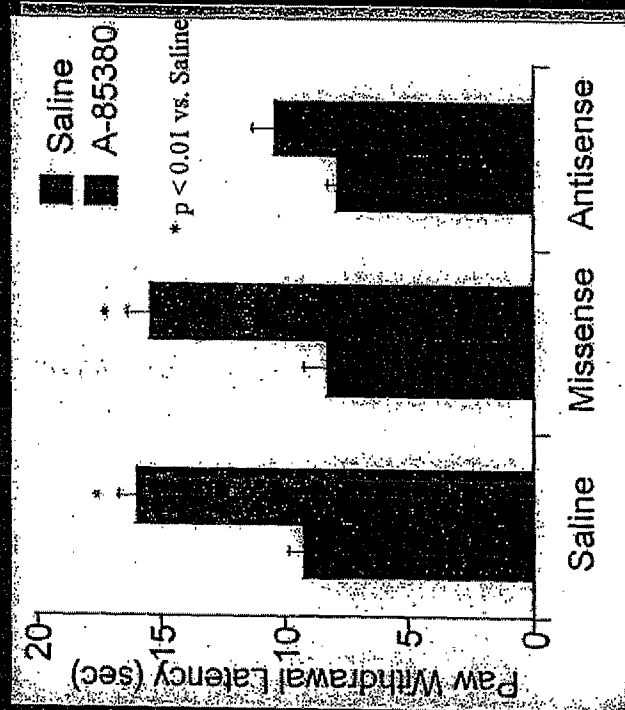
ABBT 0002378

# NNRs for Pain: Target Validation Using $\alpha 4$ Antisense

## *$\alpha 4$ Antisense Treatment Attenuates Antinociception in the Hot Box Model of Acute Thermal Pain*

• Rats received either a saline, missense, or antisense continuous i.c.v. infusion (0.75 nmol/hr) for 7 days

• Rats were evaluated in a crossover design in the hot box model of acute thermal pain



Bitner, et. al, *Brain Res.* 871: 66, 2000

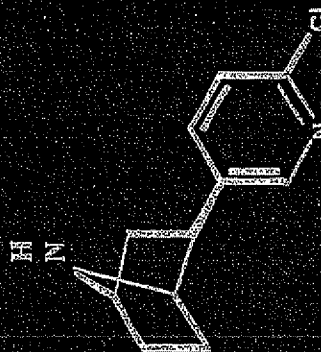
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ABBT 0002377



## Target Validation: NNR Agonists Are Analgesic

- NNR agonists are -
  - Antinociceptive (capable of raising nociceptive thresholds in naive animals)
  - Antihyperalgesic (capable of reversing the reduction in nociceptive thresholds following injury)
- Epibatidine (key discovery)
  - 200x more potent than morphine
  - Non-opioid
  - Potent NNR agonist
  - BUT highly toxic



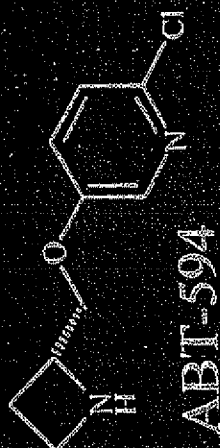
Baclo and Daly, *Mol. Pharmacol.*  
45: 563, 1994.

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ABBT 0002378

## NNRS and Pain: ABT-594

*Goal*



ABT-594

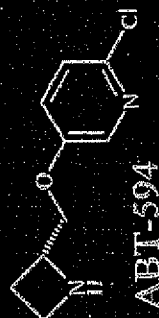
- Maintain broad spectrum analgesic efficacy of epibatidine
  - Maintain potency at  $\alpha 4$  containing NNRs
- Decrease side-effect liabilities by decreasing activity at
  - Neuromuscular junction nicotinic receptors ( $\alpha 1\beta\delta\gamma$ )
  - Ganglionic NNR subtypes ( $\alpha 3\beta 4$ ,  $\alpha 3\alpha 5\beta 2\beta 4$ )

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## ABT-594 is a More Selective NNR than Epibatidine in Radioligand Binding Studies

Binding Site (Ki; nM)	Epibatidine	ABT-594
Cytisine Binding Site ( $\alpha 4 \beta 2$ )	0.042	0.037
BTX Binding Site (Peripheral) ( $\alpha 1$ )	2.4	16,600



- ABT-594 retains potency of epibatidine at the  $\alpha 4 \beta 2$  binding site
- ABT-594 is > 5000-fold less potent than epibatidine at the peripheral neuromuscular junction nicotinic receptor

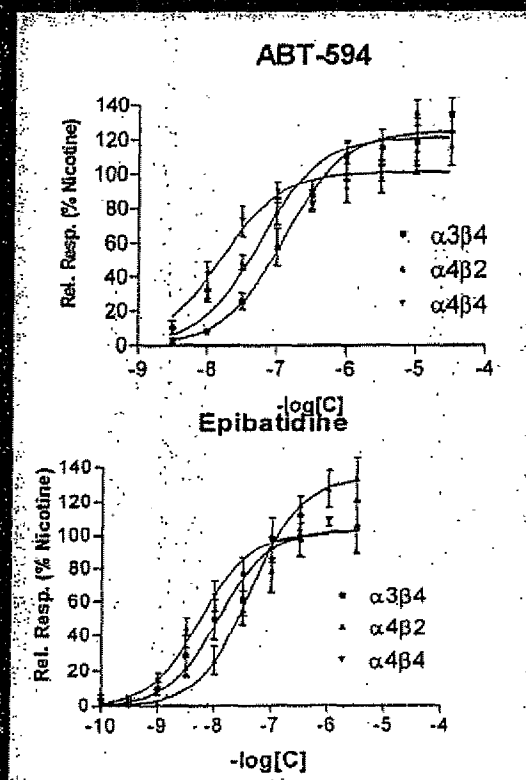
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ABBT 0002380

# In Vitro Functional Profiles of ABT-594 and Epibatidine

## Functional Activity

- Rank order of potency
  - ABT-594:  $\alpha 4\beta 4 \sim \alpha 4\beta 2 > \alpha 3\beta 4$
  - Epibatidine:  $\alpha 4\beta 4 \sim \alpha 3\beta 4 \sim \alpha 4\beta 2$
- ABT-594 displays modest  $\alpha 4$  vs  $\alpha 3\beta 4$  selectivity
  - Compounds with greatly improved selectivity have been identified

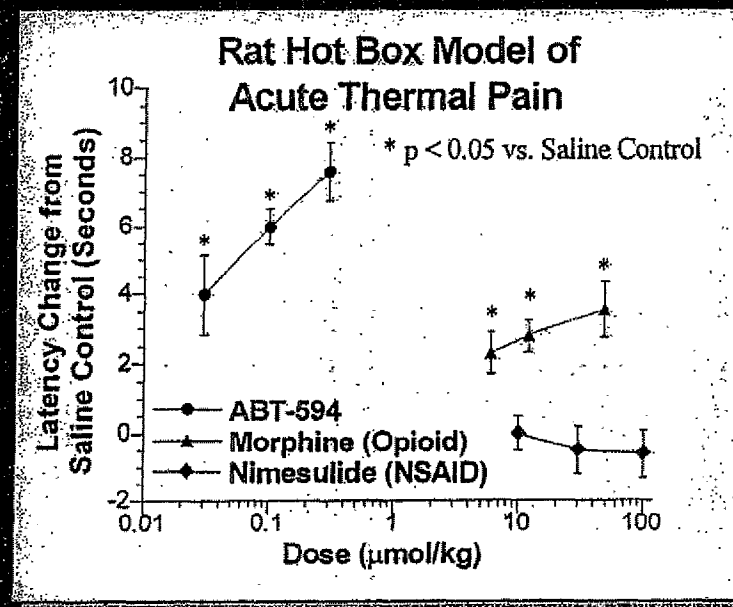


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ABB 0002381

# ABT-594: In Vivo Efficacy in Models of Acute Thermal Pain

- ABT-594 is potent and efficacious in the Hargreaves Hot Box model of thermal nociception
- Onset of Efficacy = < 30 min
- Duration of efficacy ~ 2 hrs
- The effects of ABT-594 are blocked by the nicotinic antagonist mecamylamine, but not by the opioid antagonist naloxone



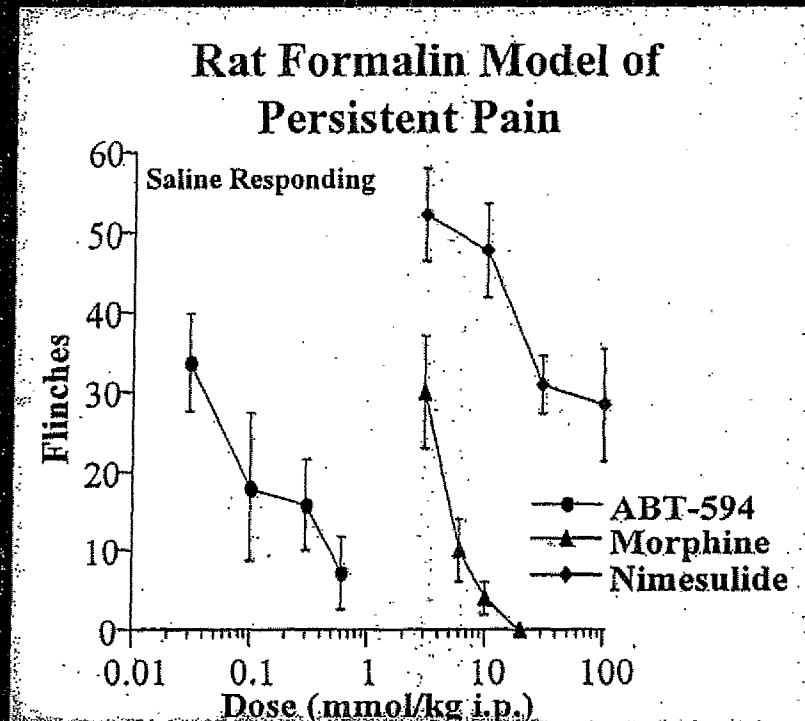
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## ABT-594: In Vivo Efficacy in Models of Persistent Pain

- ABT-594 exhibits comparable efficacy and 50-fold greater potency than morphine in Phase II of the formalin model of persistent chemical pain
- ABT-594 is active upon both i.p. and oral administration

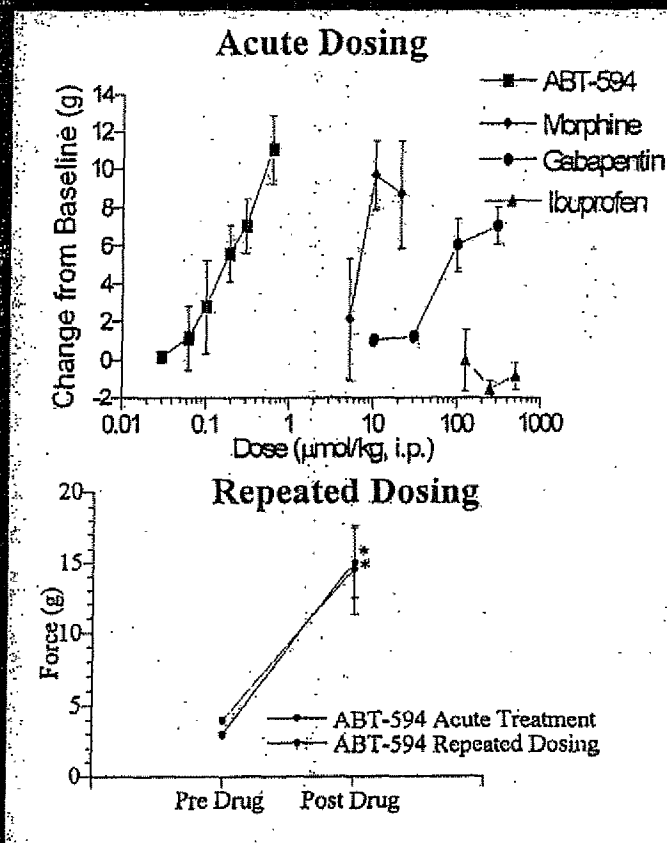


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ABB 0002363

## ABT-594: In Vivo Efficacy in Models of Neuropathic Pain

- ABT-594 exhibits comparable efficacy and enhanced potency vs. known efficacious agents in models of neuropathic pain
- Efficacy observed at  $\sim 3$  ng/ml
- ABT-594 retains efficacy following repeated administration
- Efficacy observed in rodent model of diabetic polyneuropathy



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## ABT-594: Efficacy vs. Other Analgesics

	Inflammatory Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 $\mu$ mol/kg)	+++ (0.1 $\mu$ mol/kg)	+++ (0.03 $\mu$ mol/kg)
Celecoxib	++ (30 $\mu$ mol/kg)	+ (30 $\mu$ mol/kg)	0
Morphine	+++ (3 $\mu$ mol/kg)	+++ (10 $\mu$ mol/kg)	++ (3 $\mu$ mol/kg)

+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

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## How do NNR Agonists Produce Analgesia?

- Mouse knockouts support role of  $\alpha 4$  and  $\beta 2$ 
  - Key differences between pain type
- Role for  $\alpha 4$  subtype in acute thermal pain (activation of descending inhibitory pathways)
  - Antisense studies
  - Site injection studies
  - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

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## ABT-594: Preclinical Assessment of Side Effect Liabilities

- Emesis
  - Emesis observed in monkey at 9x efficacious plasma levels
  - Emesis observed in dogs at efficacious plasma levels
  - Ferret model developed in response to early clinical data
  - Correlation established between activity at  $\alpha 3\beta 4$  NMRs and emesis
- CV
  - No effects on hemodynamics at 30X efficacious plasma levels
- Dizziness: no validated preclinical models exist
  - Effects on balance, coordination and muscle strength (Edge Test) observed following acute but not repeated dosing
- ABT-594 displays a reduced propensity for morphine-like side effects of:
  - Constipation
  - Respiratory Depression
  - Sedation

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ABT 0002387

## ABT-594: Summary of Preclinical Findings

- ABT-594 is effective across a broad range of preclinical models of acute, persistent and neuropathic pain
- ABT-594 retains efficacy upon repeated dosing
- The antinociceptive properties of ABT-594 are modulated via activation of NNRs and not via opioid receptors
- Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
  - Constipation
  - Respiratory depression
  - Sedation
- Preclinical studies suggest that ABT-594 will have an improved side-effect profile relative to nicotine

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**ABT-594 Project Review**

**February 2, 2001**

**Clinical Overview**

**Bruce McCarthy**

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**ABBT 0002389**

## ABT-594

### *Take Home Messages*

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
  - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

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ABT-594

**Definitely NOT a take home  
message for today:**

*ABT-594 will satisfy the unmet medical need  
in pain management*

*ABT-594 will not satisfy the unmet medical  
need in pain management*

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ABBT 0002391

ABT-594

## Clinical development

- Current pain management
- Development strategy: bench to bedside
- Clinical trial results

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# Classification of Pain

## Pain Categories

### Noiceptive

#### Acute

Post-dental & post-surgical Pain  
Trauma  
Pancreatitis  
Infections

#### Chronic

Osteoarthritis  
Rheumatoid arthritis  
Fibromyalgia  
Chronic visceral pain

### Neuropathic

#### Acute

Compression neuropathy

#### Chronic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug induced polyneuropathy  
HIV predominantly sensory neuropathy  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
CRPS type I and II  
Atypical facial pain  
Phantom limb pain

Cancer pain  
Back pain

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# Classification of Pain

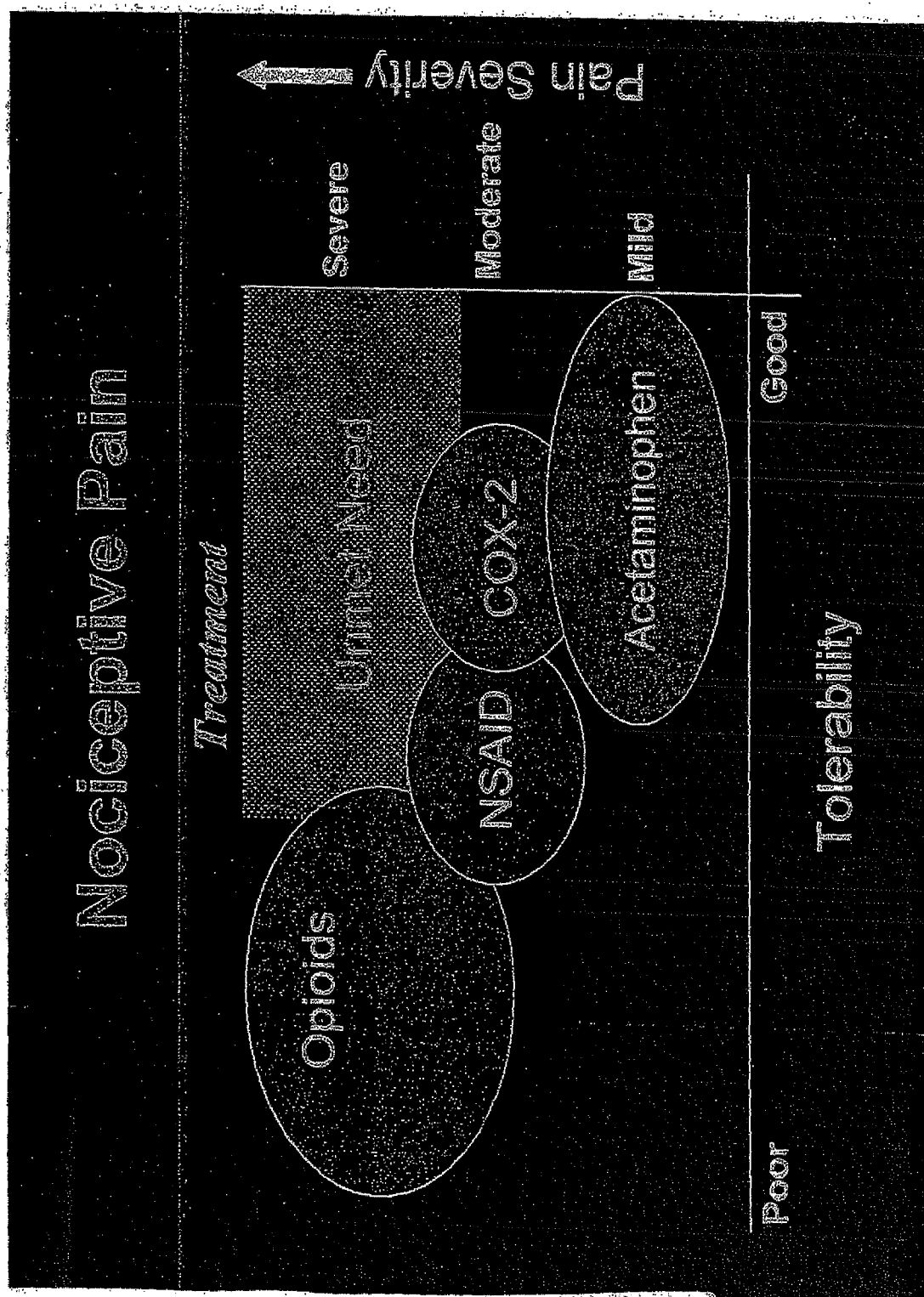
## *Pain Epidemiology*

### • Chronic pain

- 20% U.S. population: any chronic
- 22% worldwide: persistent pain

### • Neuropathic pain

- 20% of diabetics
- 40% of HIV infected
- 36% of cancer



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# Nociceptive Pain

## Treatment Adverse Events

OxyContin  
Osteoarthritis  
20 mg q12

OxyContin<sup>2</sup>

Ultram<sup>1</sup>  
50-100 mg

Event

Somnolence

N/A

23%

27%

Dizziness

31%

13%

20%

Nausea

34%

23%

41%

Vomiting

13%

12%

23%

Constipation

33%

23%

32%

Pruritis

N/A

N/A

16%

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

N/A - Not Available

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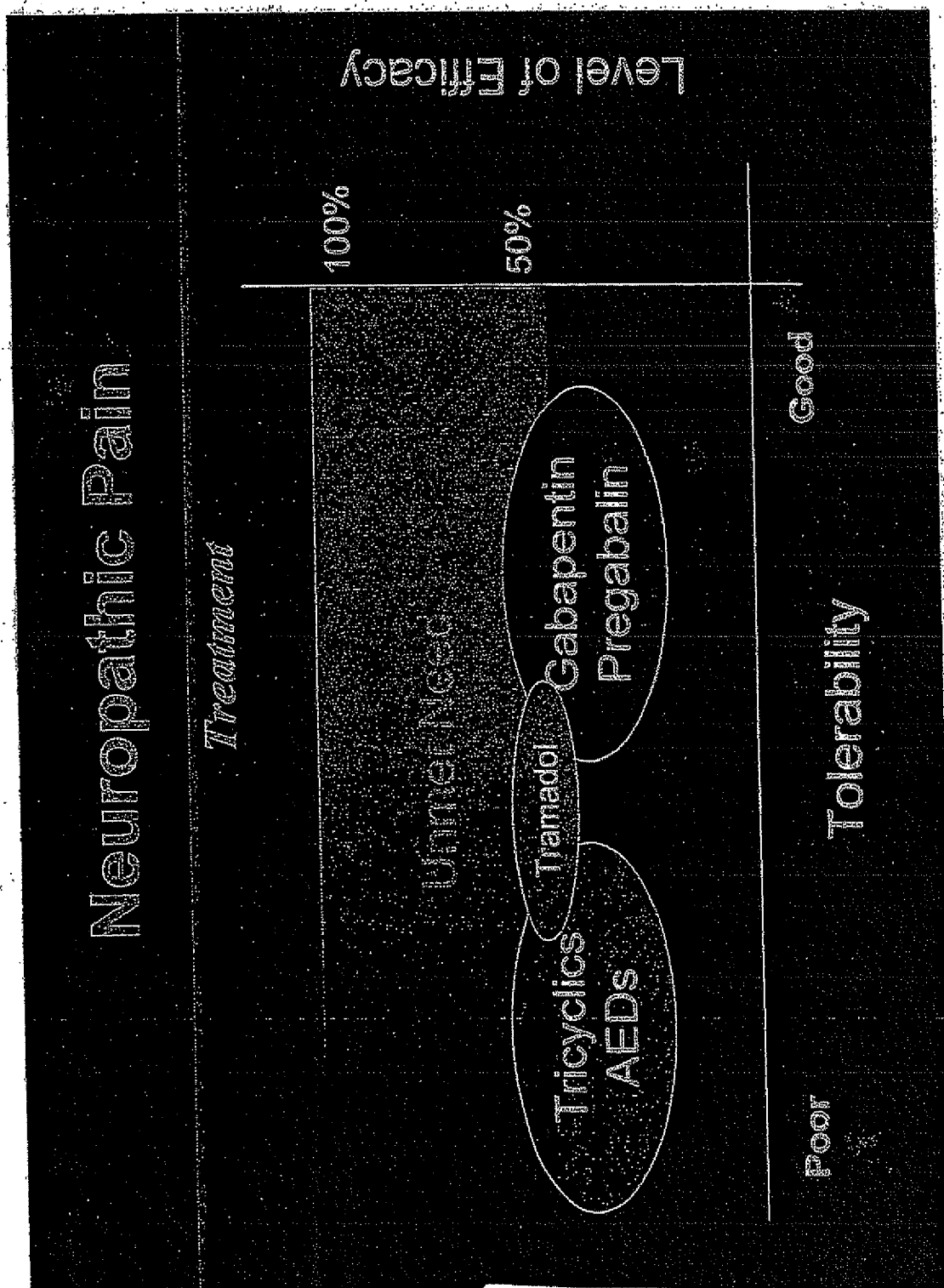
# Neuropathic Pain

## *Overview*

- Characteristic symptoms
  - Spontaneous: dysesthesia, shooting pains
  - Evolved: allodynia, hyperpathia
- Pathophysiology
  - Associated with peripheral nerve injury
  - Abnormalities develop over time in the PNS and CNS
- Treatment
  - Tricyclic and other "antidepressants"
  - Antiepileptic drugs
  - Sodium channel blockers (lidocaine)
  - Opioids
  - All minimally effective

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# Neuropathic Pain

## Treatment Adverse Events Rates

Amitriptyline 150 mg/d<sup>1</sup>      Carbamazepine 600 mg/d      Gabapentin 3600 mg/d      Pregabalin 300 mg/d

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d
Confusion	N/A	N/A	8%	5%
Somnolence	66%	53%	23%	24%
Dizziness	28%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

<sup>1</sup> Max, 1987 (n=29)  
N/A - Not Available

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ABBT 0002399



## ABT-594

### Clinical development

- Current pain management
- ❖ Development strategy: bench to bedside
- Clinical trial results

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ABBT 0002400

**ABT-594**

*Proof of Principle*

**What characterizes an innovative analgesic?**

**Spectrum of activity**

**Time of onset/duration**

**Level of efficacy**

**Safety/efficacy ratio**

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**ABBT 0002401**



# ABT-594

## *Spectrum of Activity: Where to Start?*

### Acute

Post-dental surgery  
Sprains and strains  
Acute back pain  
Trauma  
Post-general surgery  
Post-orthopedic surgery  
Dysmenorrhea  
Renal colic  
Biliary colic  
Pancreatitis  
Infections

### Neuropathic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug-induced polyneuropathy  
HIV predominantly sensory neuropathy  
Back pain  
Cancer pain  
Trigeminal neuralgia  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
Complex regional pain syndromes (I, II)  
Atypical facial pain  
Phantom limb pain

### Chronic Nociceptive

Osteoarthritis  
Chronic back pain  
Rheumatoid arthritis  
Cancer pain  
Fibromyalgia  
Sickle cell disease  
TBI disorder  
Bursitis  
Tendinitis  
Chronic visceral pain

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ABT-594

*Choose Portals of Entry*

Acute Pain



Molar  
Extraction

Neuropathic Pain



Peripheral  
Neuropathy

Chronic Nociceptive  
Pain



Osteoarthritis

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ABT 0002403

# ABT-594

## *Initial Profile*

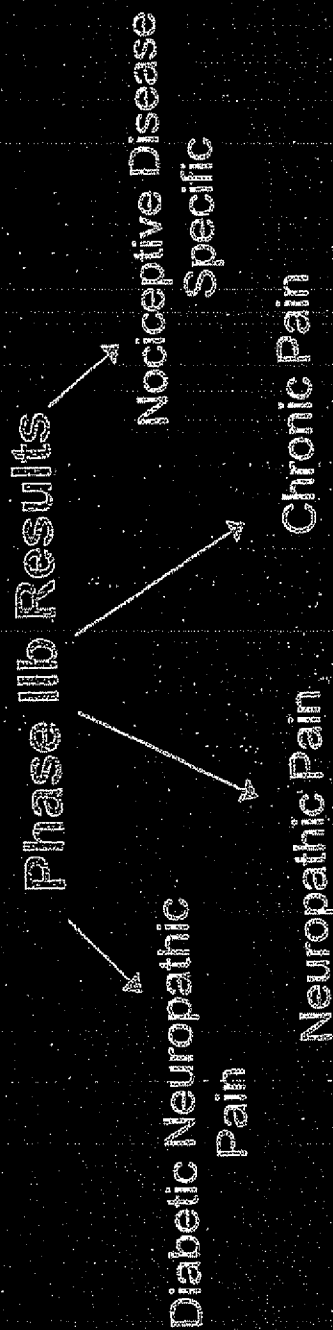
- **Preclinical promise**
  - Efficacy for all types of pain
  - Challenges
- **Current characteristics**
  - Analgesic potential demonstrated in molar extraction, neuropathic pain and osteoarthritis
  - Onset ( $T_{max}$ , tolerability) appears to exclude rapid relief of pain ("acute pain")

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ABBT 0002404

# ABT-594

## *Future Regulatory Strategy*



### +/- Publication Strategy/Phase IV (e.g.)

- Post-herpetic neuralgia
- Nociceptive pain
  - o Osteoarthritis
  - o Low back pain

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ABBT 0002406

## ABT-594

### Clinical development

- Current pain management
- Development strategy: bench to bedside
- Clinical trial results

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ABBT 0002406

## ABT-594

### *Pharmacokinetics and Metabolism*

- Half-life ( $t_{1/2}$ ): about 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{max}$  similar with/without food
- $T_{max}$  varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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**ABT-594**

**ABT-594's analgesic potential demonstrated in:**

**Molar Extraction**

**Neuropathic Pain**

**Osteoarthritis**

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**ABBT 0002408**



# Molar Extraction Study

## Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo

Single dose

- Third molar extraction
- Outcome measures:
  - Pain relief (PR)
  - Categorical scale:
 

0	1	2	3	4
none	a little	some	a lot	complete
- Power: 70% to detect an effect similar to acetaminophen plus codeine Solution


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# Molar Extraction Study

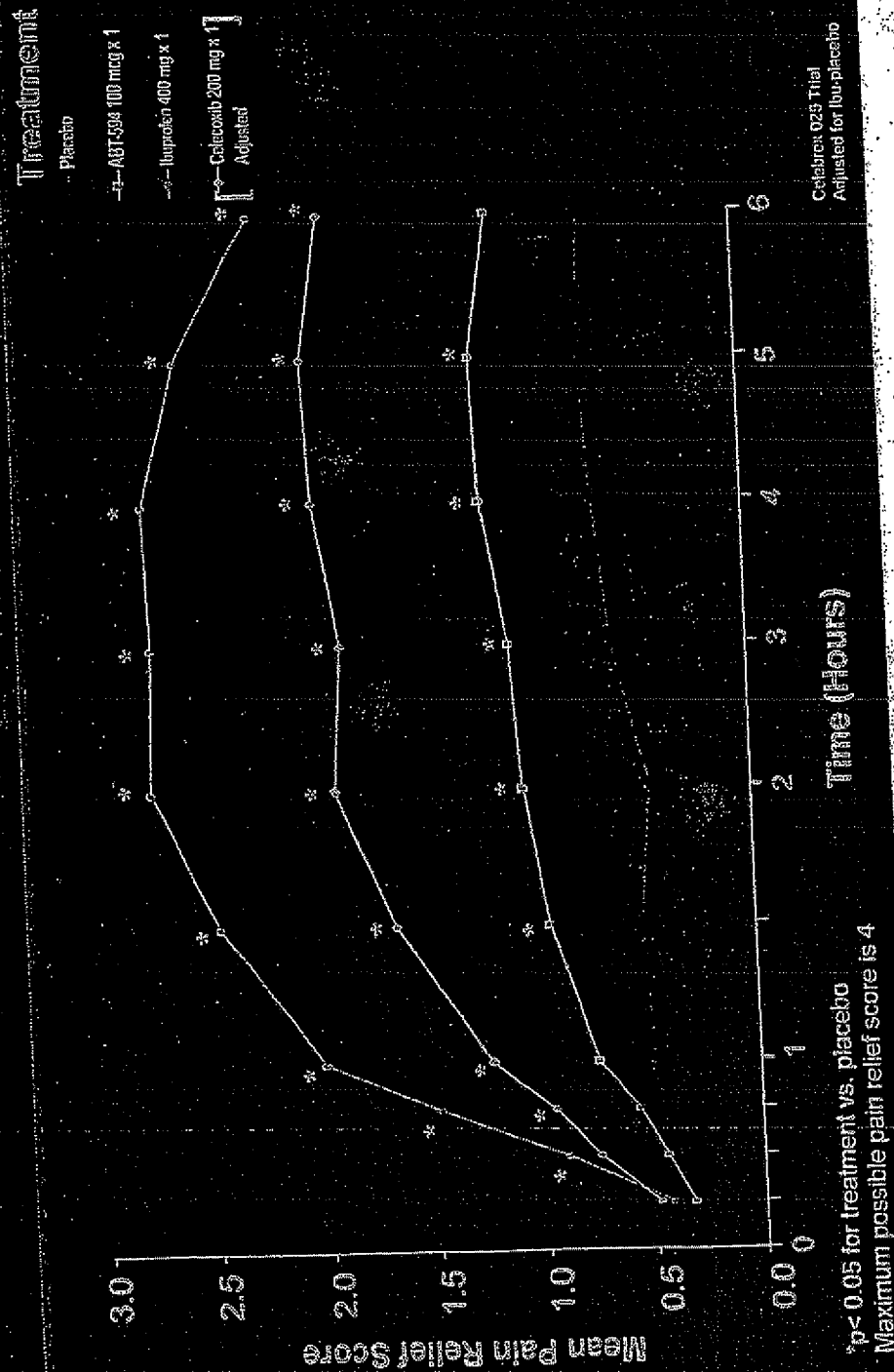
## Outcome Measures

<ul style="list-style-type: none"> <li>Pain Relief (PR)           <ul style="list-style-type: none"> <li>Categorical scale:</li> </ul> </li> </ul>	0	1	2	3	4
	none	a little	some	a lot	complete
<ul style="list-style-type: none"> <li>Total Pain Associated Relief (TOTPAR)           <ul style="list-style-type: none"> <li>Area under the curve for PR (0-6 hours)</li> </ul> </li> </ul>					
<ul style="list-style-type: none"> <li>Pain Intensity (PI)           <ul style="list-style-type: none"> <li>Categorical scale:</li> </ul> </li> </ul>	0	1	2	3	
	none	mild	moderate	severe	
<ul style="list-style-type: none"> <li>Visual Analog Scale</li> </ul>					
<ul style="list-style-type: none"> <li>Stop Watch Model           <ul style="list-style-type: none"> <li>Time to "perceptible" and "meaningful" relief</li> </ul> </li> </ul>					
<ul style="list-style-type: none"> <li>Time To Rescue Medication</li> </ul>					
<ul style="list-style-type: none"> <li>Patient Global           <ul style="list-style-type: none"> <li>Rate medication:</li> </ul> </li> </ul>	1	2	3	4	
	poor	fair	good	excellent	

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ABBT 0002410

# ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



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ABBT 0002411

# Neuropathic Pain Pilot

## Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
  - 52% idiopathic
  - 46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

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ABBT 0002412

# Neuropathic Pain Pilot

## Outcome Measures

### • Pain Intensity (PI)

– Categorical Scale:

0 none 1 mild 2 moderate 3 severe

– Visual Analog Scale:  
(0-100 mm)

no pain ————— worst possible

### • Neuropathic Pain Scale (NPS)

– 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

The most sharp sensation imaginable ("like a knife")

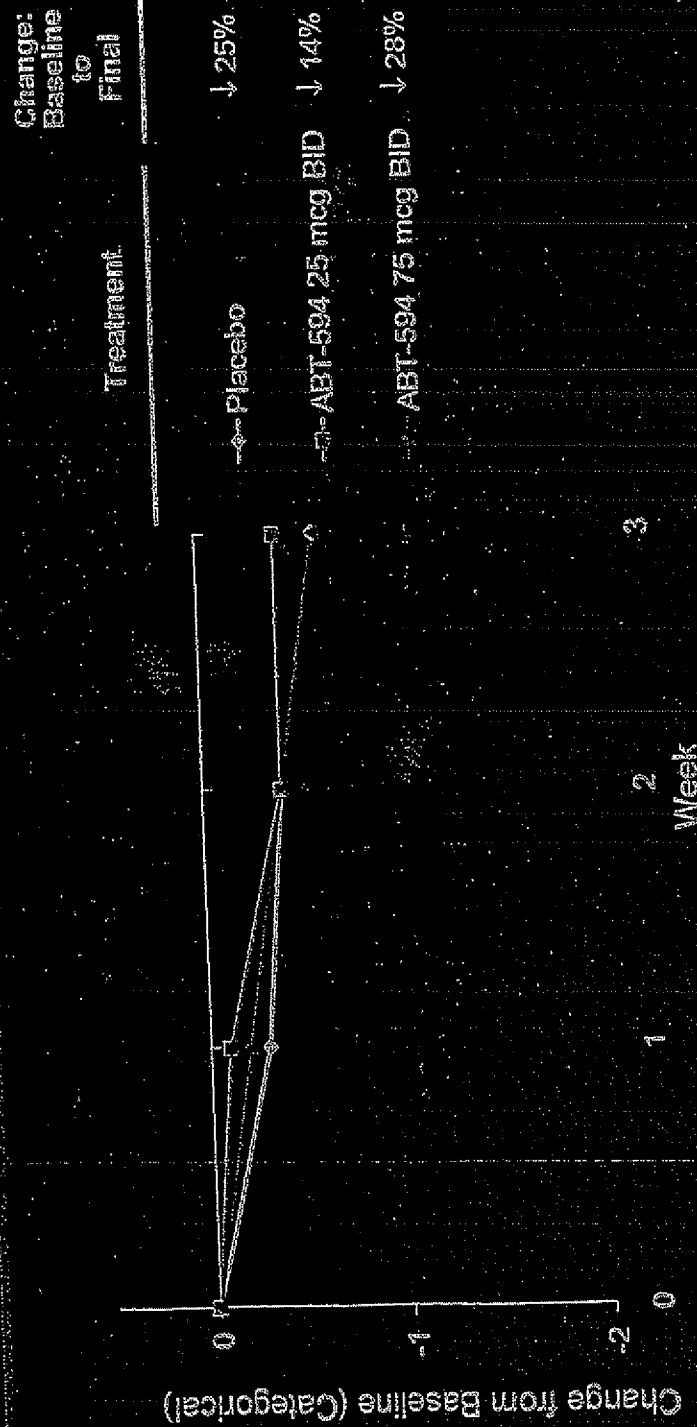
not sharp 1 2 3 4 5 6 7 8 9 10

### • Patient Global (PG)

– Rate Medication:

1 poor 2 fair 3 good 4 excellent

# ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared to Placebo in Neuropathic Pain



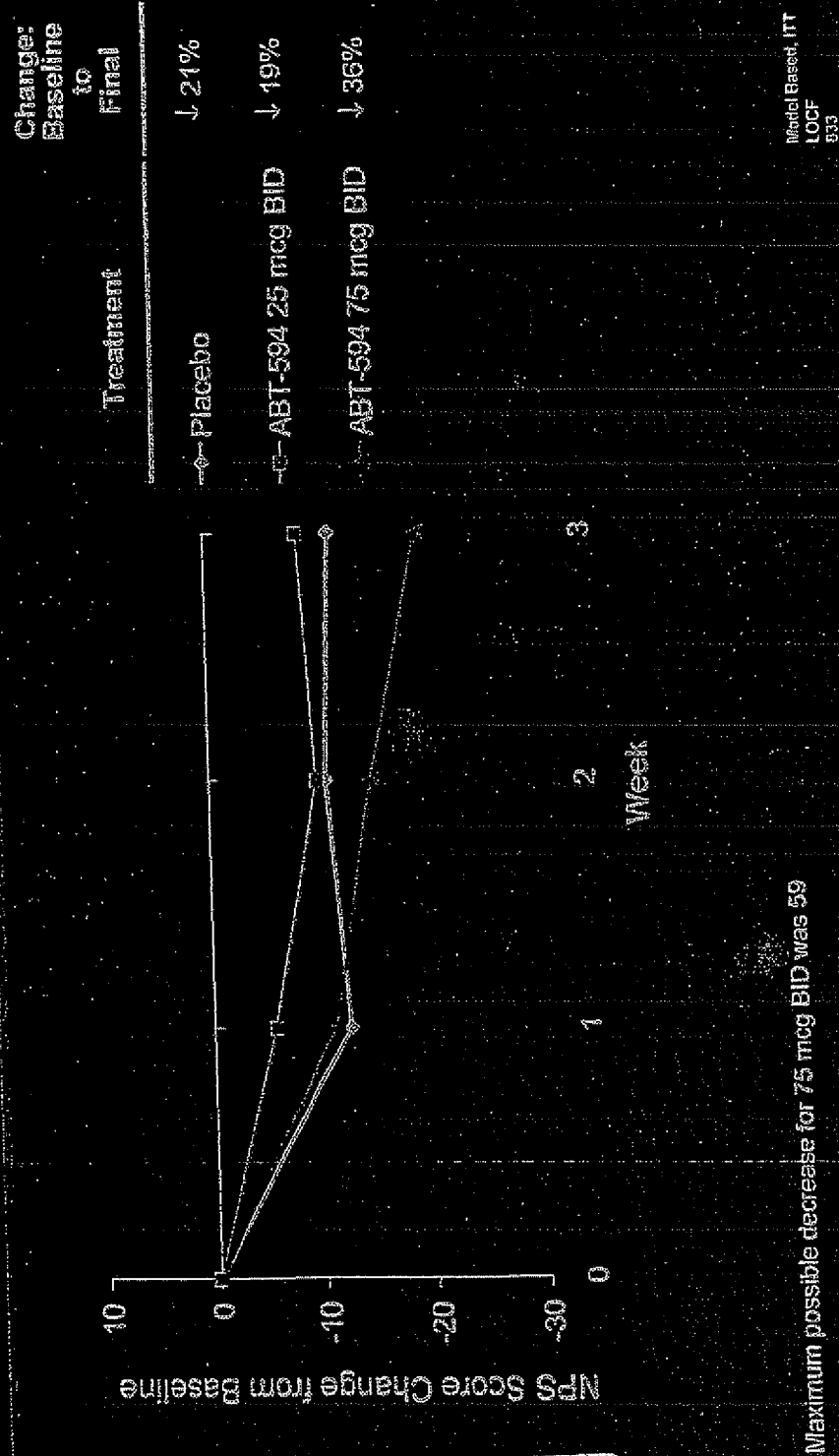
Model based, ITT  
LOCF  
833

Maximum possible decrease for 75 mcg BID was 2.5

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ABBT 0002414

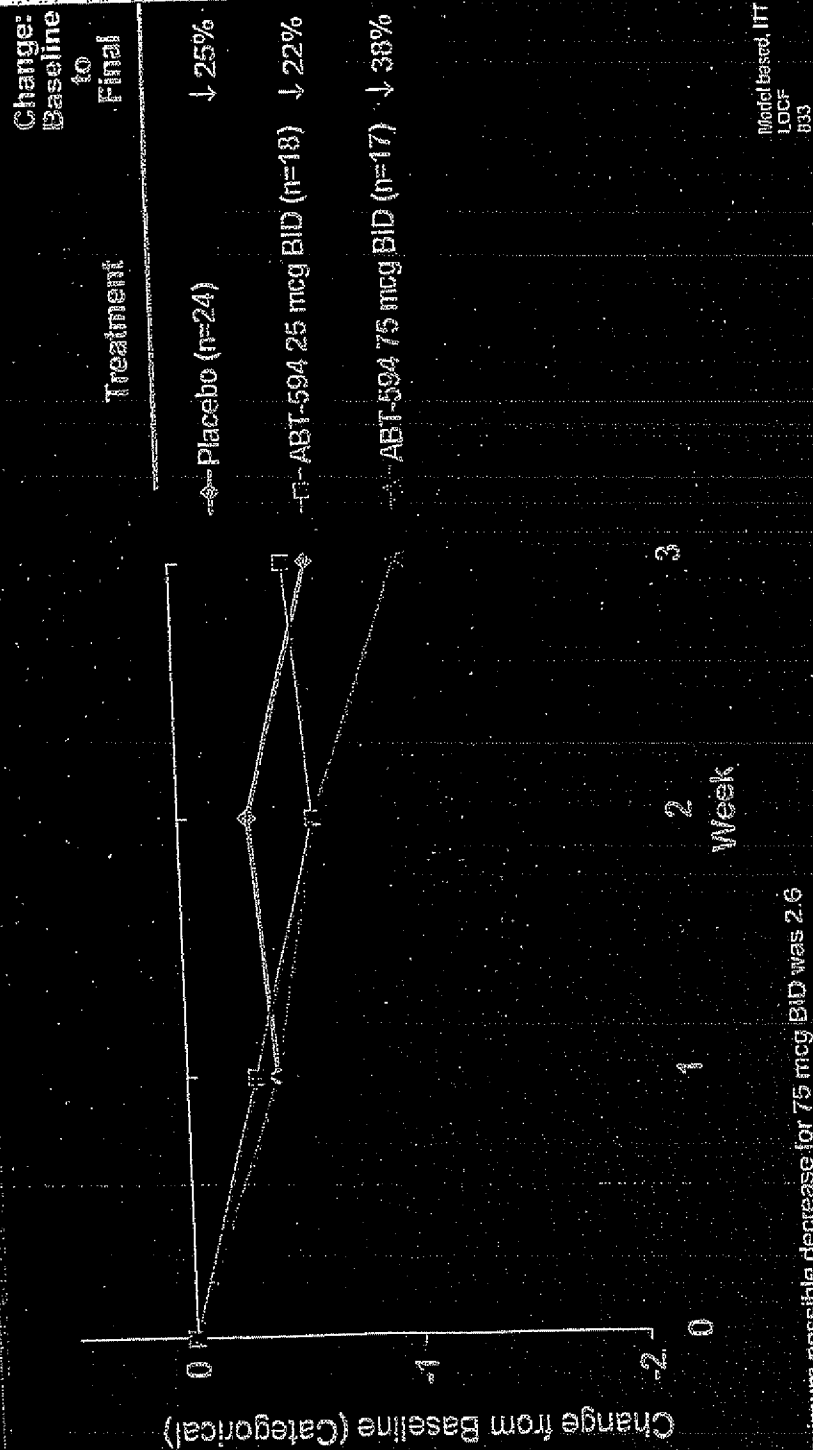
# ABT-594 75 mcg BID Reduces the NPS More Than Placebo



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# ABT-594 75 mcg BID Reduces Daily Pain Score More Than Placebo in Diabetic Polyneuropathy

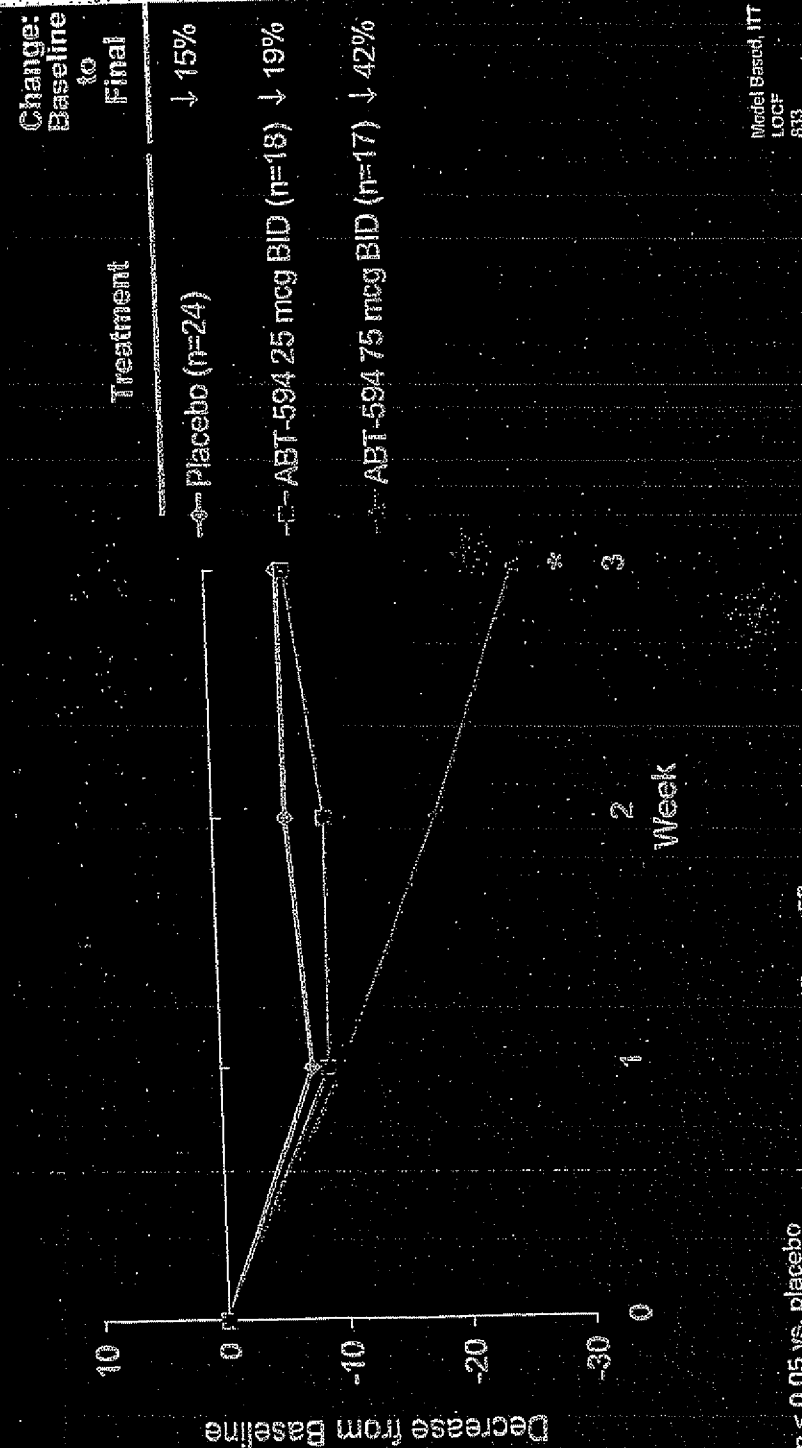


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ABBT 0002416



# ABT-594 75 mcg BID Significantly Reduces NPS Compared to Placebo in Diabetic Polyneuropathy



\* p ≤ 0.05 vs. placebo  
Maximum possible decrease for 75 mcg BID was 52.

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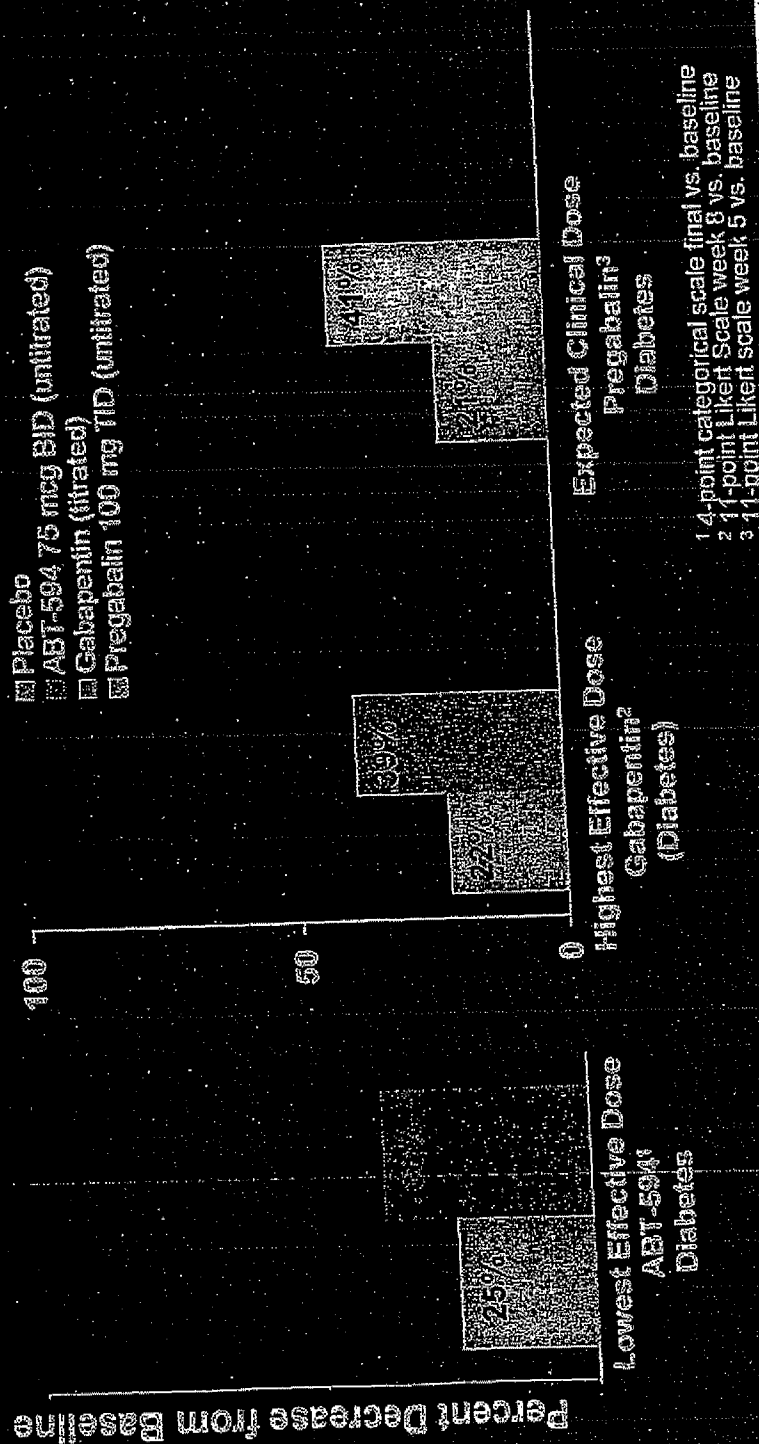
ABBT 0002417



# ABT-594 75 mcg BID has a Similar Effect To Gabapentin

## ABT-594 vs. Gabapentin and Pregabalin

■ Placebo  
 ■ ABT-594 75 mcg BID (untitrated)  
 ■ Gabapentin (titrated)  
 ■ Pregabalin 100 mg TID (untitrated)



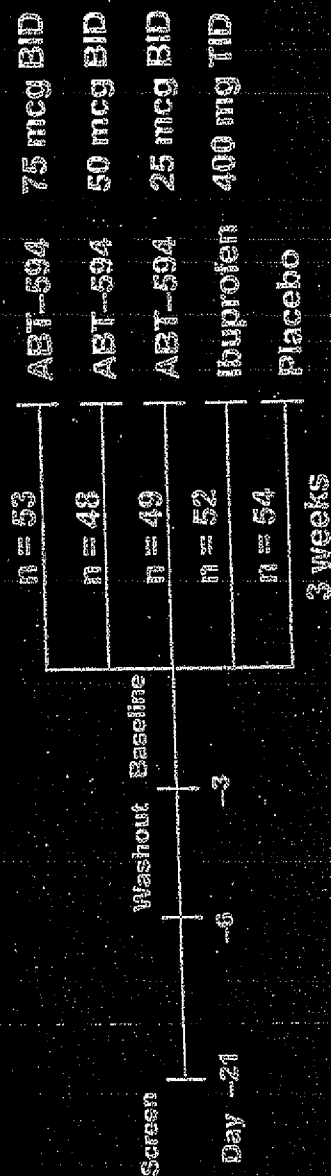
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ABBT 0002418

# Osteoarthritis Pain Pilot

## Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)

- Soft Elastic Capsule

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CONFIDENTIAL

ABBT 0002419

# Osteoarthritis Pain Pilot Study

## Outcome Measures

### • Pain Intensity (PI)

– Categorical Scale:

0	1	2	3
none	mild	moderate	severe

– Visual Analog Scale (VAS):

no pain ————— worst possible

### • WOMAC

– Pain (0-500)

– Stiffness (0-200)

– Function (0-1700)

Total (0-2400)

### • Patient Global

– Rate Medication:

1	2	3	4
poor	fair	good	excellent

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ABBT 0002420

# Osteoarthritis Pain Pilot Study

## WOMAC

### Pain

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain |

extreme  
pain

### Stiffness

How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness |

extreme stiffness

### Function

What degree of difficulty do you have...

- Descending stairs?
- Rising from bed?

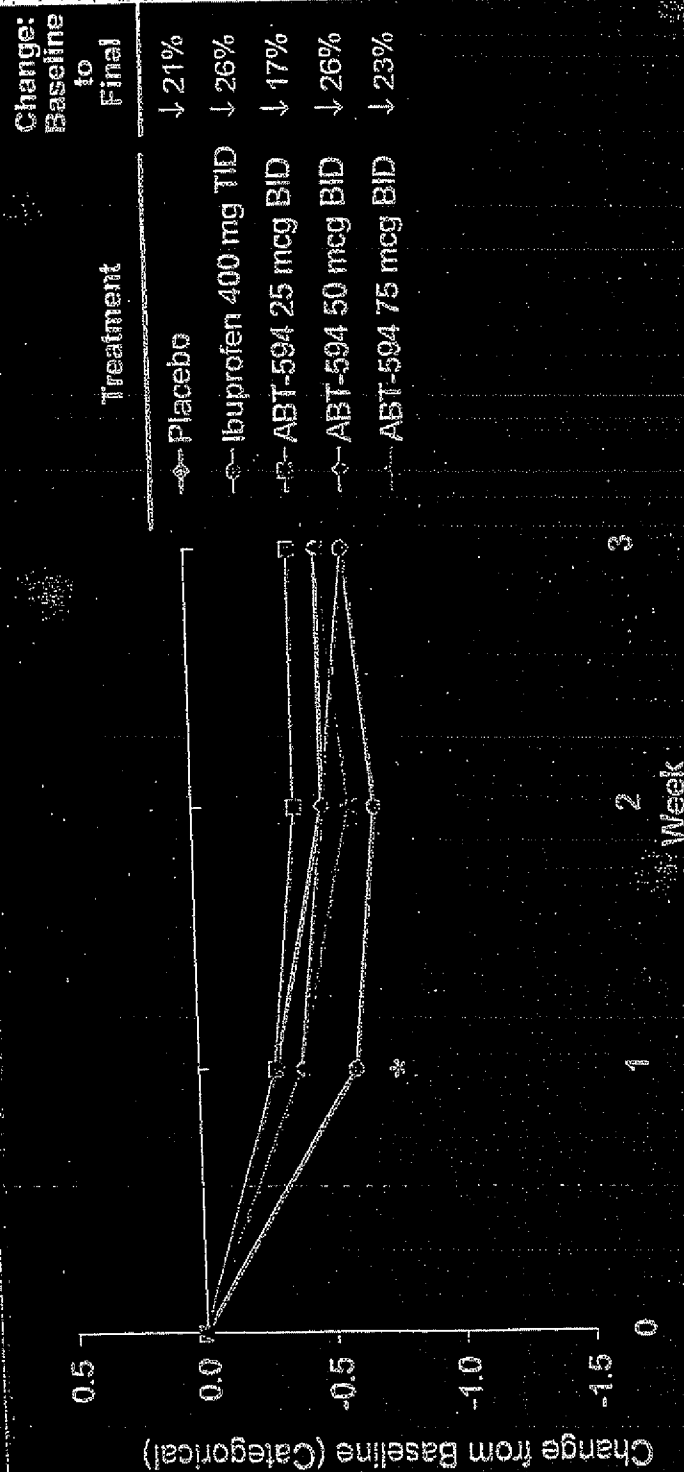
no difficulty |

extreme difficulty

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ABBT 0002421

# ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared To Placebo in Osteoarthritis



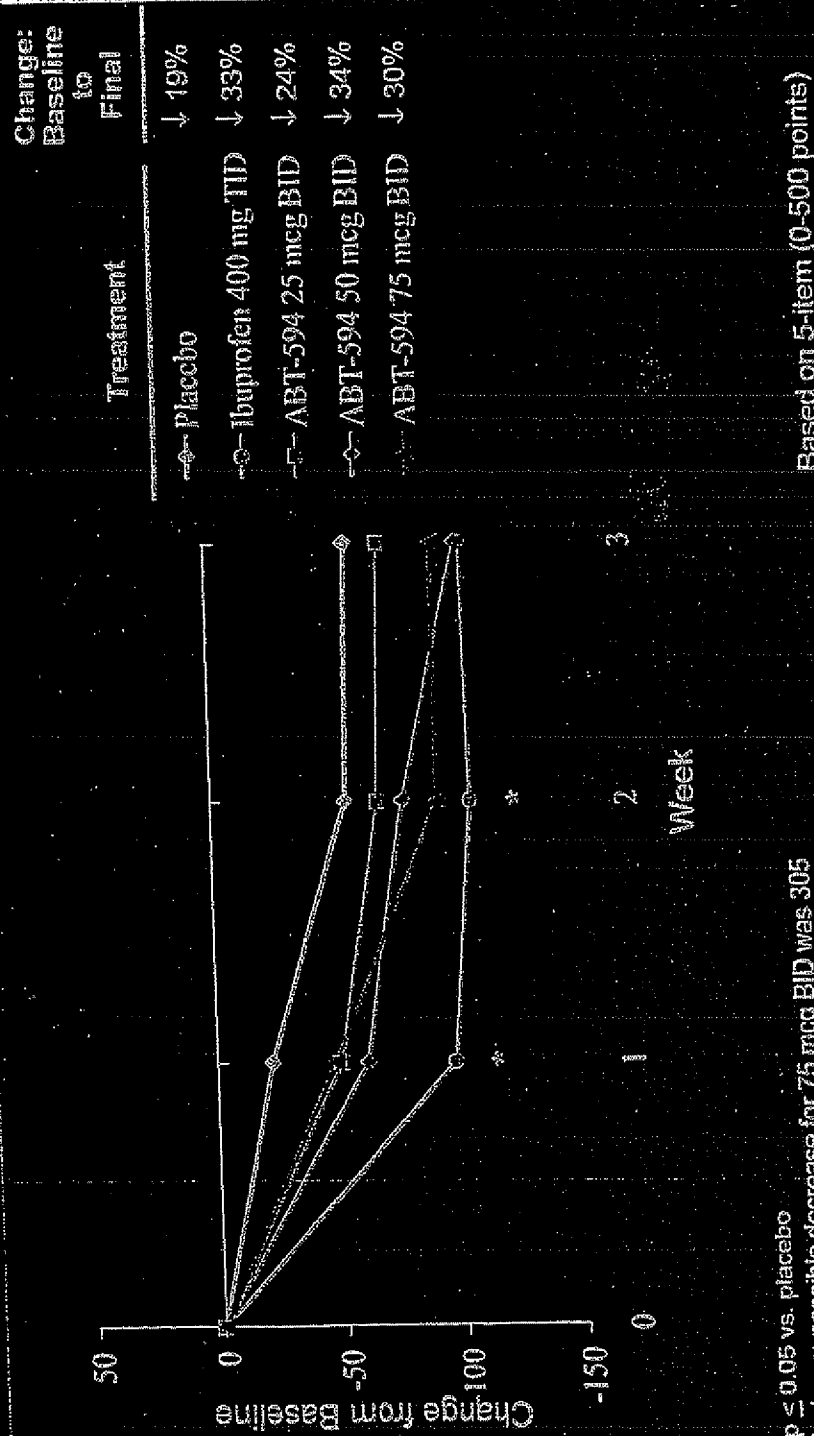
Merck-based, ITT  
LOCF  
826

\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 2.2

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ABBT 0002422

# ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis



\* p ≤ 0.05 vs. placebo  
Maximum possible decrease for 75 mcg BID was 305

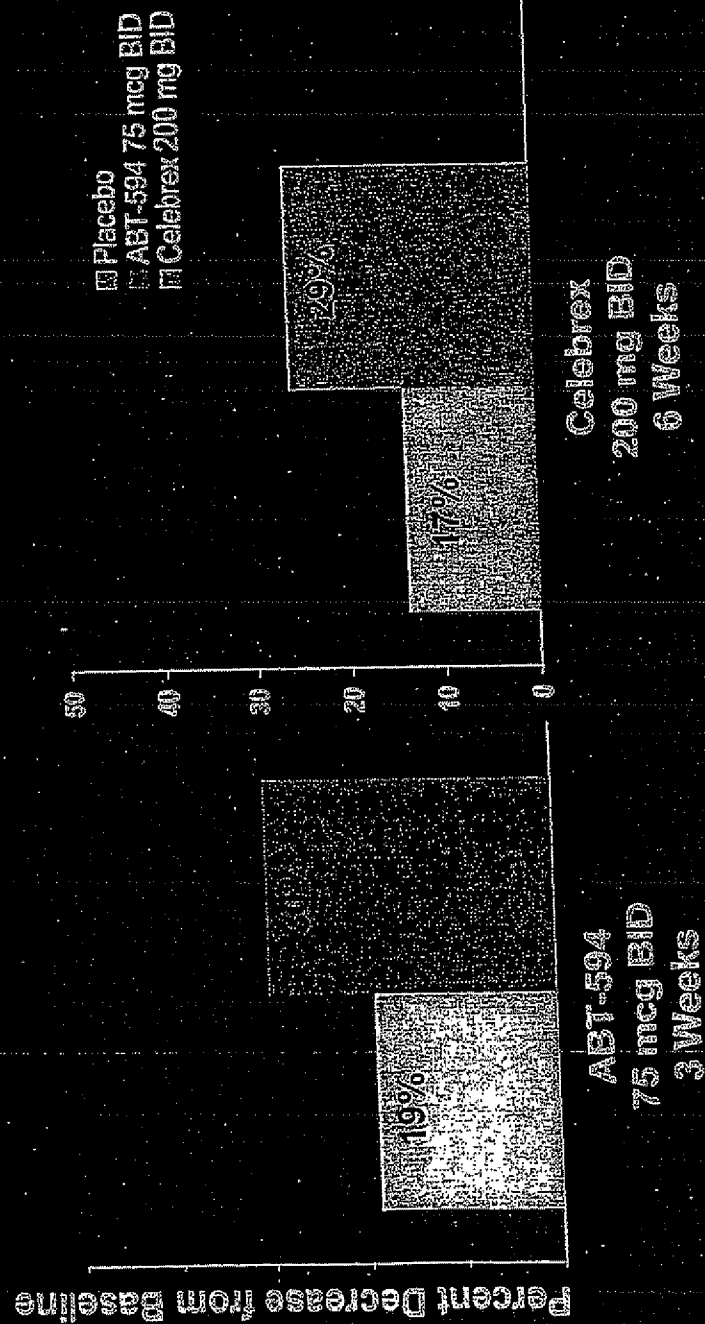
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ABBT 0002423



# ABT-594 75 mcg BID Has An Effect Similar to Celebrex

*WOMAC Pain Decrease from Baseline*



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ABBT 0002424

## ABT-594

### *Phase IIIa Efficacy Conclusions*

- Analgesic Potential Demonstrated
- Molar Extraction
  - Significance vs. placebo starting at 1.5 hours
- Neuropathic Pain
  - 75 mcg BID may be lowest effective dose for patients with painful diabetic polyneuropathy
- Osteoarthritis Pain
  - 75 mcg BID may be lowest effective dose as judged by the WOMAC pain sub-score

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ABBT 0002426



# ABT-594 Safety

## *Phase IIIa Adverse Events*

### • Characteristic AEs

- Nausea
- Vomiting
- Dizziness

- AEs attenuate after repeated administration

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ABBT 0002426

## Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	3%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	3%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	N/A

<sup>1</sup> Max, 1987 (n=29)<sup>2</sup> M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002427

# Adverse Event Rates for Select Analgesics

Event	Ultram <sup>1</sup> 50-100 mg q4-6h	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12h	ABT-594 <sup>3</sup> 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	24%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

<sup>3</sup> M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002428

## ABT-594

### *Phase IIa Conclusions*

- Analgesic potential demonstrated
- Phase IIa studies included inadequate dose ranging
  - SEC tolerated better than predicted by solution
  - 75 mcg BID (HGC) very well tolerated vs. other analgesics
  - Two Phase I studies (M99-076 and M99-120) showed:
    - 300 mcg BID HGC tolerated
    - Titration may improve tolerability
- Full analgesic potential should be defined with adequate dose ranging studies in Phase IIb

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ABBT 0002429

## Phase IIIb

- Trials

- Neuropathic Pain (M99-114)

- Ongoing

- Osteoarthritis Pain (M99-115)

- Unfunded

- Doses

- 150, 225, 300 mcg BID

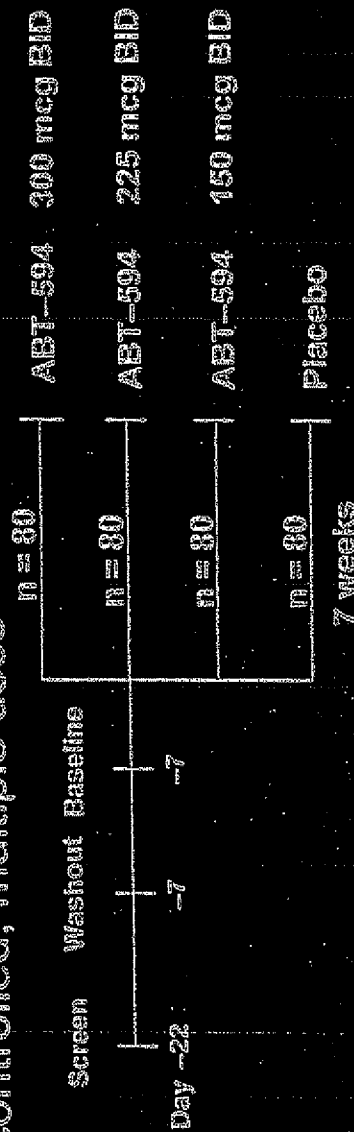
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ABBT 0002430

# W99-114: Neuropathic Pain

## Design

- 320 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-Day primer phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I to detect 39% ABT-594 improvement, 25% placebo (ES 0.46)
- Hard Gelatin Capsule

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ABBT 0002431

## M99-114: Neuropathic Pain

### *Outcome Measures*

- Primary

- Weekly average of daily pain (11-point Likert in a diary)

- Secondary

- Site-based pain scale (11-point Likert)
- Neuropathic Pain Scale
- Patient Global Impression of Change
- Physician Global Impression of Change
- SF-36

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ABBT 0002432



## M99-114 Status

- Enrollment
  - Ended 1/5/01 at 269 subjects
  - Pre-specified power not reached
  - Width of confidence intervals not meaningfully different between 269 and 320 enrolled
- Database release -- 5/01
- Go/No Go -- 6/01

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ABBT 0002433



## ABT-594

### *Take Home Messages*

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
  - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

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ABBT 0002434

**ABT-594 Project Review  
February 2, 2001  
Commercial Assessment**

**Andrea Landsberg**

**Laura Robinson**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002435**

## ABT-594 Commercial Assessment: Key Take Aways

- Neuropathic pain market is the primary target
  - Underserved market with significant unmet need
  - ABT-594 has potential to be first novel drug in decades indicated for neuropathic pain
- Additional opportunity in “chronic persistent pain” market
- Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets

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## Neuropathic Pain Market: Sales

	2000 US Sales (\$MM)	2000 ex-US Sales
AEDs	\$299	\$190
TCAs	\$3	\$45
OPIOIDS	\$37	NA
OTHERS	\$85	\$45
TOTAL	\$424	\$280

US Sales factored for neuropathic pain and annualized  
Vs Prior Year: US Growth est 20%, ex-US growth est 10%

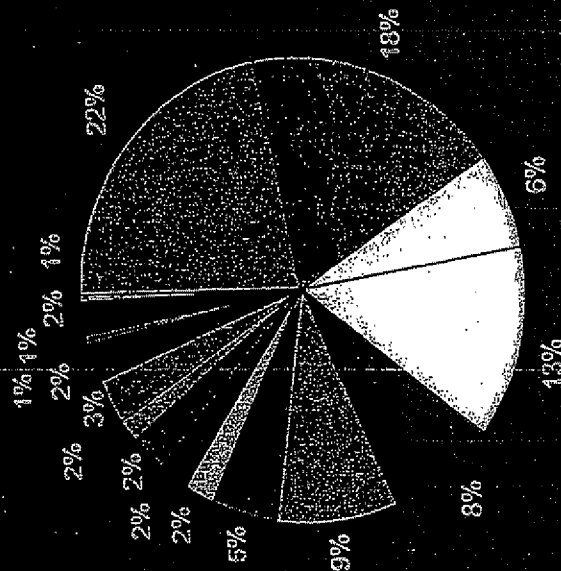
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ABBT 0002437

# Drug Classes Used to Treat Neuropathic Pain

*Dispersed market due to limited promotion and lack of dominant effective product*

SEIZURE DISORDERS
ANTIARTHRITIS SYS PLN
COX-2 INHIBITORS
CODEINE & COMB NON-INJ
CORTICOSTS PLAIN INJ
ANTIDEP TR/TETRA
PTY ANALGESICS
PYRIDOXINE (VIT B6)
SYN NON-NARC NON-INJ
MUSC RLX W/O ANALG
CORTICOSTS PLAIN ORAL
PROPOXYPHENES
ANESTH INJECT LOCAL
ASPIRIN, APC, ETC
SSRI'S/SNRI'S
ACETAMINOPHEN
BENZODIAZEPINES



**Drug Uses Data (not Rx or \$'s)**

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## Use in Neuropathic Pain

- Even if target only 'focused' indication in 'painful, diabetic neuropathy' expect trial and usage in all types of neuropathic pain
  - Neurontin use all off-label
  - Carbamazepine is indicated for trigeminal neuralgia but used in all neuropathic pain
  - Generally held premise that NP likely has some similar mechanisms across etiologies (reinforced by current drug usage)

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## Market Opportunities in Neuropathic Pain

- Improved efficacy
  - Partial pain relief is the norm
  - Polypharmacy often required to manage pain
- Improved responder rates
  - Typically only 40% to 60% of patients respond to any given treatment
- Improved tolerability over time
  - TCAs, AEDs, opioids have troublesome SEs that do not diminish over time
- Dose reduction
  - Most TCAs and AEDs (including Neurontin) typically dosed TID
- Titration reduction
  - TCAs and AEDs require >2 weeks titration period to minimize SEs or reach effective dose

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ABBT 0002440

## Chronic Persistent Pain (CPP) “Spillover”

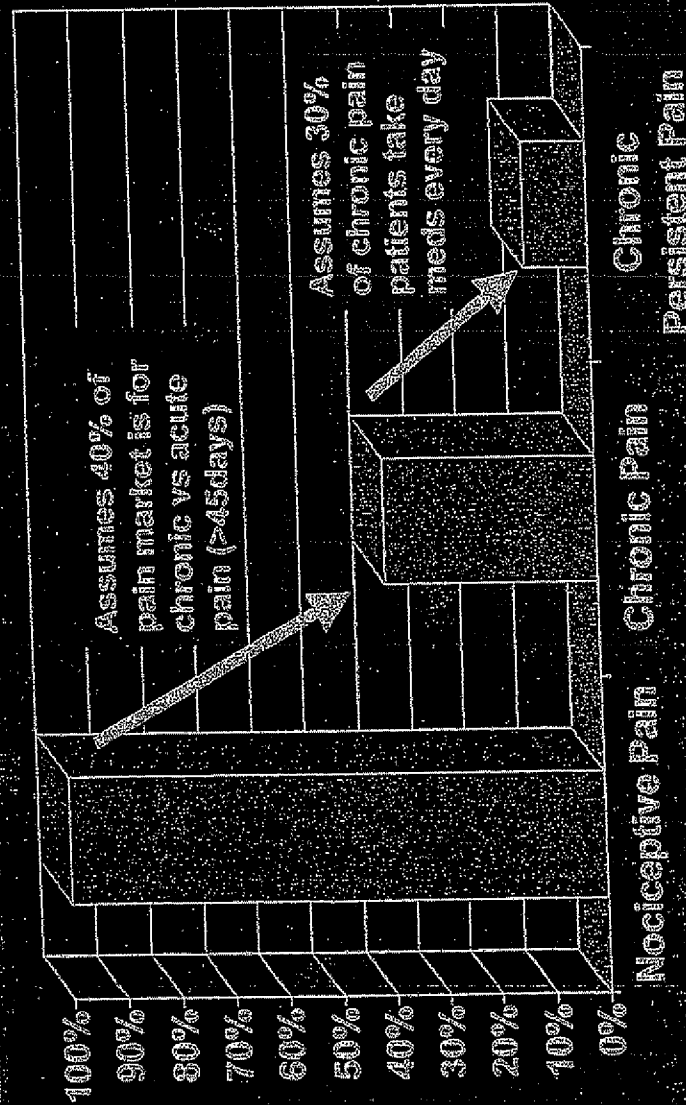
- Onset of action and need for titration limits ABT-594 to a small segment of the nociceptive pain market
- CPP = Chronic persistent pain conditions for which patients are on daily medications, over extended periods of time (vs. PRN, or ‘as needed’, consumption)

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ABBT 0002441



# Chronic Persistent Pain



IMS Longitudinal Data indicates over 30% of pain meds filled for >=30 days  
Quantitative primary market research indicates that >60% of chronic pain patients take meds every day

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ABBT 0002442

## Chronic Persistent Pain Market

	1999 Sales (\$MM)	CAGR (97-99)	Rxs (MM)	CAGR (97-99)
US	\$700	5%	35	1%
Ex-US	\$680	8%	58	3%

### CPP Market Size Assumptions:

Assume 40% of opioid, non-opioid, COX-2 market is for chronic pain and 30% of that is 'persistent', i.e.: medication taken every day

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ABBT 0002443

# Qualitative Market Research Results

Profile		Share of Patients		
Efficacy	AEs vs. current agents	OA	RA	Low-back

*Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain*

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ABBT 0002444

# Qualitative Market Research Results

Profile		Share of Patients		
		OA	RA	Low-back
Efficacy	AEs vs. current agents			
Better	Equivalent			
Same	Equivalent			
Better	Poor			

TCAs used as "benchmark" efficacy in NP

Tolerability vs. current agents: equivalent = 5% nausea; 5% vomiting; 10% dizziness; poor = 20% nausea; 10% vomiting; 30% dizziness

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ABBT 0002445

# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent	19%	12%	16%
Same	Equivalent	15%	8%	10%
Better	Poor	12%	6%	11%

Spillover market share in chronic persistent pain markets (in forecast, assuming only 5% share)

MR did not test impact of titration on market share

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ABBT 0002446



# Qualitative Market Research Results

Profile		Share of Patients
Efficacy	AEs vs. current agents	Neuropathic Pain
Better	Equivalent	31%
Better	Poor	24%
Same	Equivalent	27%

Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain

In forecast assuming 20% share of NP

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ABBT 0002447

## Neuropathic Pain Pipeline

- Pregabalin is in Phase III, but questions remain regarding Pfizer's Neurontin/Pregabalin strategy
- 4 NNR preclinical programs appear to be targeting pain indications; ABT-594 is much further along
- Other new AEDs may have potential for treatment of neuropathic pain and are conducting phase IV trials; unclear whether these agents will pursue an NP indication
- Several novel pain mechanisms being explored
  - Calcium channel blockers
  - Sodium channel blockers
  - NMDA antagonists

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ABBT 0002448

## Positioning of ABT-594 in Neuropathic Pain

- Greater efficacy than AEDs and TCAs in NP
- Better long term tolerability (than TCAs and opioids)
- Safe in all patient populations
- Convenient BID dosing with simple, short titration period
- No tolerance over time and non-scheduled
- Limited drug interactions
- Novel mechanism of action

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ABBT 0002449



## Positioning of ABT-594 in CPP

- Effective alternative to opioids with:
  - No tolerance, respiratory depression, constipation, etc.
  - Non-scheduled
- For patients receiving insufficient relief with current therapies or NSAID/opioid intolerant patients
- Better efficacy than COX-2s with novel mechanism of action and no major safety issues

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ABBT 0002460

# ABT-594 Global Forecast Ranges

(\$MM)

	Peak Sales		
	Low	Base	High
US	\$92	\$339	\$509
Ex-US	\$130	\$363	\$712

- NP shares: 5%, 20% or 30%
- CPP shares: 3%, 5%, 7%

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ABBT 0002451

## Key Product Challenges

- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*
  - *Neurontin/Pregabalin may have advantage*
    - *Will need to minimize early DCs as much as possible*
  - *Potentially low therapeutic index*
- *Titration*
  - *Schedule must be as short and simple as possible*
- *Nicotinic mechanism*
  - *Will require pre-launch market education and priming to diffuse negative associations and generate interest surrounding novel MOA*

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ABBT 0002462

Go/No Go Process

Bruce McCarthy

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ABBT 0002463

# ABT-594

## *Go/No Go Process*

### The Challenge

Integration of many interrelated data

Efficacy

Safety

Dose Response

Pharmacodynamics

Dose Selection

Phase III Trial Design

Titration Effects

Indications

Market Research

Segmentation

Targeting

Positioning

### The Plan

Leverage decision analysis (DSG) as a process  
to determine Go/No Go criteria

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ABBT 0002454

## ABT-594

### *Go/No Go Process*

#### **Process to include:**

1. Scope and frame issues and process
2. Analysis of M99-114 and other clinical data
3. Dose identification
4. Draft Phase III trial design
5. Market research
6. Valuation
7. Presentation and asset strategy: 6/01

Decision Analysis

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ABT-594

*Go/No Go Process*

What will a "Go" decision look like?

Patients and physicians will have  
compelling reasons to choose ABT-594 vs.  
other analgesics for the relief of pain

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ABBT 0002456

**ABT-594 Project Review**

**February 2, 2001**

**Follow-On Strategy**

**Mike Meyer**

**HIGHLY  
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**ABBT 0002457**



# Identification of ABT-594 Backup

## *Clinical Results Outline Specific Improvements Required for Backup*

- Ernesis
  - Modeled preclinically in ferret and dog
- Nausea
  - Ferret model can qualitatively address nausea index
- Dizziness
  - Mouse rotarod
  - Rat Edge test

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ABBT 0002458

## Discovery Program Basis

### *NNR Subtypes Differentially Mediate Efficacy and Side Effects*

- Different NNR subtypes mediate analgesic effects of nicotinic agonists and adverse events
- Program committed to the identification of NNR subtype selective compounds
- Project initiated research collaboration with NeuroSearch (Denmark)
  - Access to human recombinant NNRs
  - Access to new structural classes of NNR modulators

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ABBT 0002469

## Nociception Mediated by $\alpha 4$ Subtypes

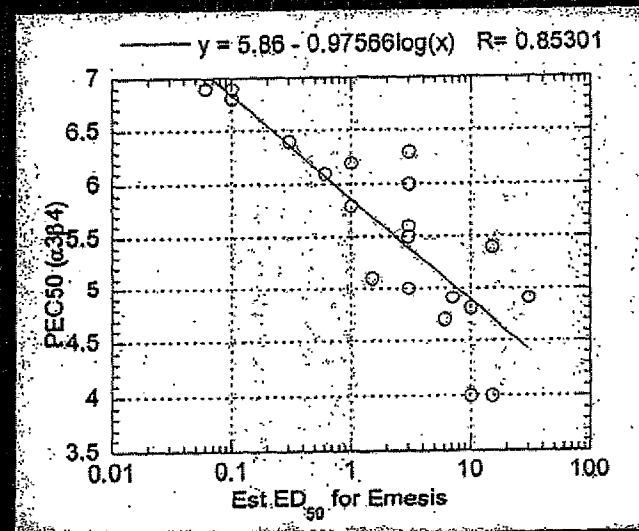
- Mouse knockouts support role of  $\alpha 4$  and  $\beta 2$ 
  - Key differences between pain type
- Role for  $\alpha 4$  subtype in acute thermal pain (activation of descending inhibitory pathways)
  - Antisense studies
  - Site injection studies
  - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

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ABBT 0002480

## Emesis Mediated by $\alpha 3\beta 4$ Subtype

- In preclinical models, emesis is correlated to potency and efficacy at ganglionic ( $\alpha 3\beta 4$ ) NNR subtypes
- Antagonist and route of administration studies suggest both local and systemic contribution



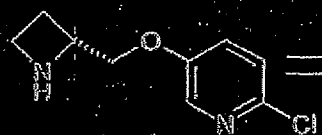
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ABB 0002461

# $\alpha 4$ -Selective Ligands: In Vitro Profile

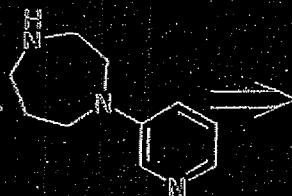
- Radioligand Binding Profile:

0.046 nM



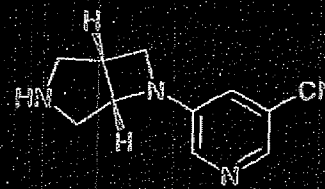
ABT-594

0.049 nM



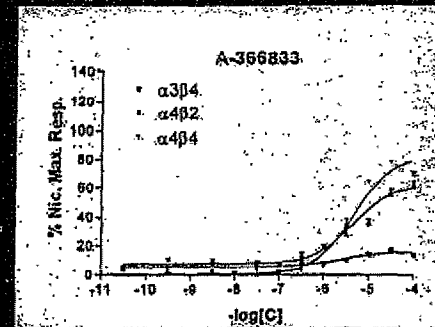
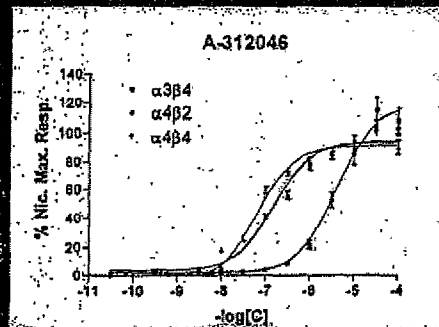
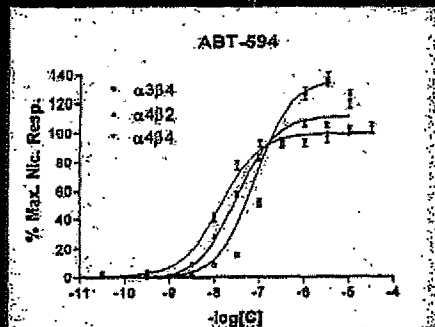
A-312046

3.19 nM



A-366833

- In Vitro Functional Profile:

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ABBV 0002482

## Analgesic Efficacy vs. ABT-594 (Rat Models)

	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
<b>ABT-594</b>	+++ (0.08 $\mu\text{mol/kg}$ )	+++ (0.1 $\mu\text{mol/kg}$ )	+++ (0.03 $\mu\text{mol/kg}$ )
<b>A-312046</b>	+++ (1.8 $\mu\text{mol/kg}$ )	+++ (0.7 $\mu\text{mol/kg}$ )	+++ (1.9 $\mu\text{mol/kg}$ )
<b>A-366833</b>	+++ (3 $\mu\text{mol/kg}$ )	+++ (5 $\mu\text{mol/kg}$ )	++ (6 $\mu\text{mol/kg}$ )
<b>Celecoxib</b>	++ (30 $\mu\text{mol/kg}$ )	+ (30 $\mu\text{mol/kg}$ )	0
<b>Morphine</b>	+++ (3 $\mu\text{mol/kg}$ )	+++ (10 $\mu\text{mol/kg}$ )	++ (3 $\mu\text{mol/kg}$ )
<b>Gabapentin</b>	+ (200 $\mu\text{mol/kg}$ )	++ (100 $\mu\text{mol/kg}$ )	0

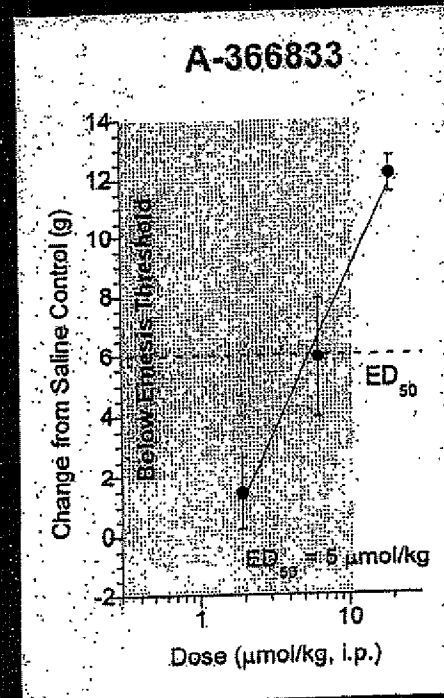
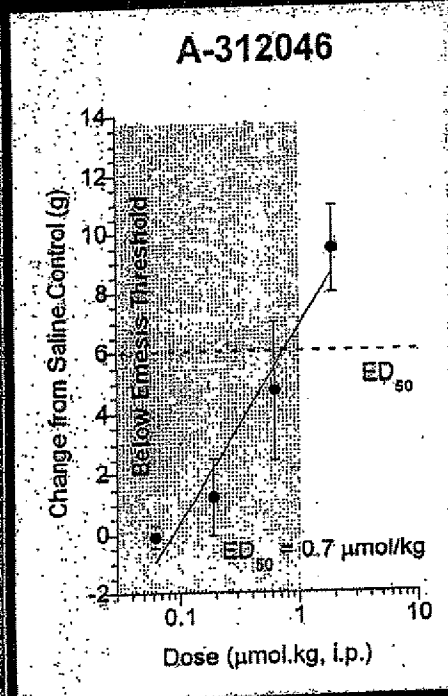
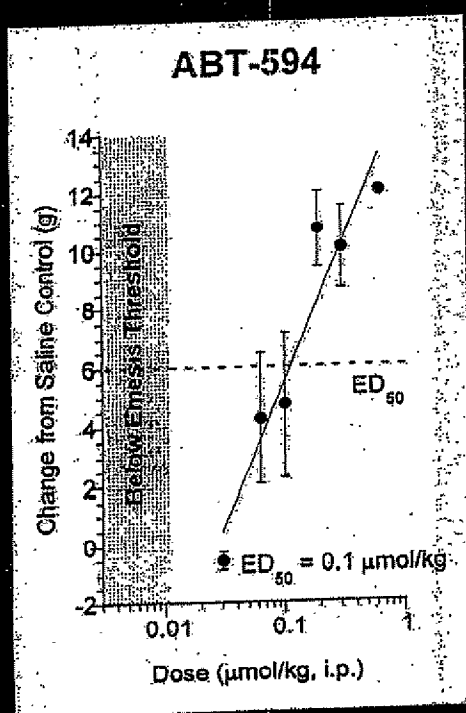
+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

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ABBT 0002483

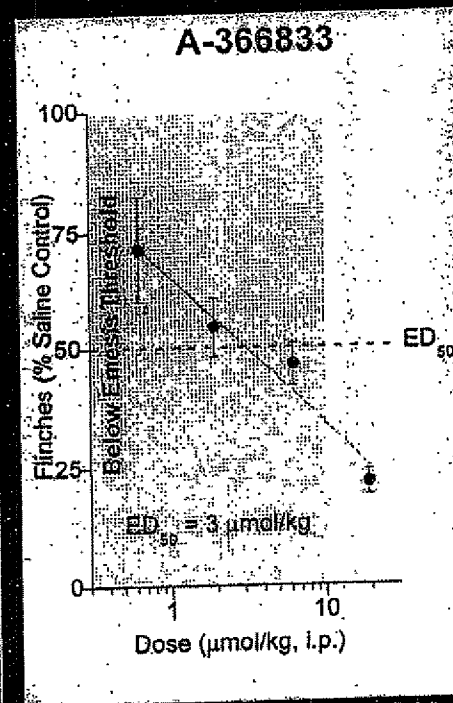
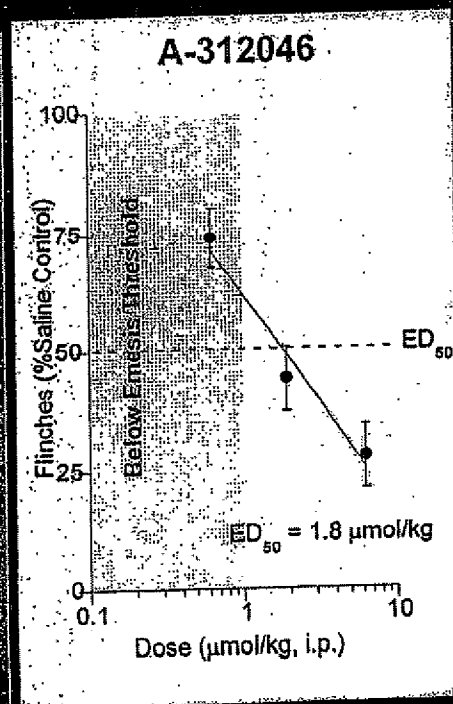
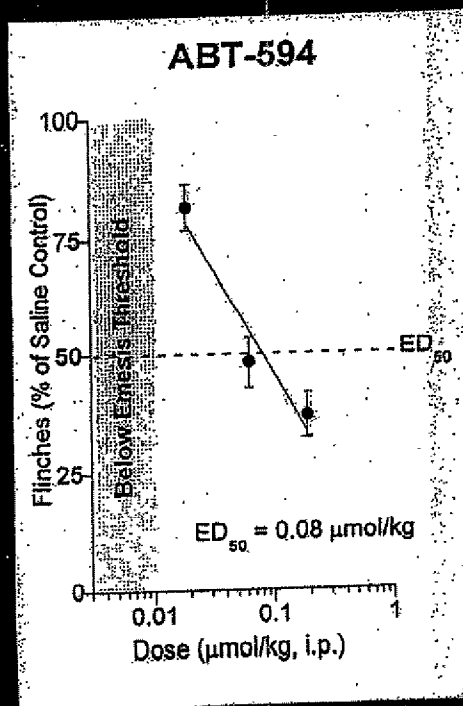


# Efficacy Indexed to Emesis Liability (Neuropathic Pain)



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ABT 0002464

# Efficacy Indexed to Emesis Liability (Nociceptive Pain)



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ABT 0002486



## Therapeutic Index Comparison

- Therapeutic index based on ratio of highest no effect dose for adverse event and  $ED_{50}$  in pain models

Adverse Event	Therapeutic Index	
	Improvement vs. ABT-594 A-312046	A-366833
Emesis (Ferret)	5 - 14x	20 - 27x
Seizure Threshold (Mouse)	4 - 11x	>11x
Edge Test (Rat)	7 - 24x	>12x

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ABBT 0002466

## Pharmacokinetics

	$t_{1/2}$	CLp	%F
Rat	1.5 h	1.7	61%
Dog	4.7 h	0.4	35%
Monkey	1.4 h	1.7	80%
Rat	3.0 h	1.95	80%
Dog	1.4 h	2.89	13%
Monkey	1.5 h	2.36	3%
Rat	1.5 h	3.02	73%
Dog	2.6 h	0.35	109%
Monkey	2.5 h	0.53	74%

ABT-594

A-312046

A-366833

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ABBT 0002467

## Additional Characterization and Ongoing Studies

- A-312046:
  - Evaluation of viability of transdermal formulation
  - Identification of prodrug analogs
- A-366833:
  - Ames and chromosomal breakage neg.
  - CEREP binding studies – no significant findings
  - Ongoing studies:
    - Evaluation in additional pain models
    - PK/PD studies – plasma levels at efficacious and emetic doses
    - Dog, monkey, human hepatocyte metabolism
    - Cardiovascular evaluation
    - Two-week toxicology in rats

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ABBT 0002468

## Backup Status

- A-366833:
  - Broad spectrum activity, but particularly effective in persistent nociceptive pain model
  - Significantly decreased side effect liability
  - Excellent oral bioavailability across three species
  - May extend into general pain indication
- A-312046:
  - Excellent activity in neuropathic pain model
  - Pharmacokinetics may preclude development as oral drug
  - Alternative formulations may be useful as backup for ABT-594 in neuropathic pain market

HIGHLY  
CONFIDENTIAL

ABBT 0002469

**PLs' EN**

Bruce  
McCarthy /LAKE/PPRD/  
ABBOTT  
02/02/2001 02:33 PM

To Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Michael  
K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H  
Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, James  
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Steve C  
cc Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, Keith F  
Hendricks/LAKE/AI/ABBOTT@ABBOTT, Rosemarie K  
Waleska/LAKE/PPD/ABBOTT@ABBOTT, John M  
Leonard/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject DSG

Liz-

Per our preliminary discussions regarding the DSG process for ABT-594 Go/No Go, here is a preliminary list of core team members (see below). Please comment on the number of core team members, as you have a better perspective on how many is too many (understanding that additional project team members will be involved whenever necessary). In addition, please comment on whether the list is sufficiently comprehensive.

When we discuss scope and frame during our first meeting, we will want to discuss several issues that came up at today's Leiden meeting (though I think these are not necessarily new):

1. Given the results of Phase IIb, what is the value of the currently identified back-ups (ie, go to back up, proceed with 594 + start back up, etc...we can steal these analyses from the SDG project 2 years ago!)?
2. What additional work should be performed to understand time to onset issues (e.g., should additional work be performed in advance of the start of phase IIb, including perhaps the development of a parenteral formulation to better understand this issue) and what actions might we take based upon the results of this additional work?
3. How does ABT-594 fit in with a comprehensive strategy to bring NNR's for pain to the market? What kind of investment should be made to achieve success for this strategy (e.g., how many back-ups should be brought forward, when, what properties should the compounds have, how many simultaneously to clinic, etc). This issue is (obviously) very large, however, my impression is that this larger strategy needs to be formulated in order to have a go/no-go discussion about ABT-594. The issue also begs for a comprehensive pain strategy at Abbott (I think this latter point is unlikely to be achieved by our analysis, but we could always try to develop one nonetheless).

After we have a final core team list, let me know how I can help to get the first meeting scheduled ASAP. As we discussed at the preliminary meeting, we look forward to your expertise in facilitating this process (DSG as powerful decision-making tool), but we (members of the discovery/development/commercial team and especially those of us in the venture) very much want to take a leadership position in driving the overall process.

Venture/Development  
Marleen Verlinden  
Chris Silber  
Bruce McCarthy  
Mike Biarnesen

Discovery  
Jim Sullivan

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ABBT314925

Hendricks DEP. EX. NO. 25  
FOR ID., AS OF 4/27/08

Mike Meyer

Regulatory

Jim Steck/David Ross (Jim and David could back each other up)  
Nigel Livesey

NPD

Laura Robinson/Rose Waleska (Laura and Rose could back each other up)

PARD

Howard Cheskin

PK

Walid Awni

Stats

David Morris/Jim Thomas

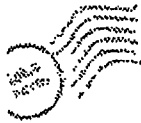
Thanks!  
Bruce.

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ABBT314926

**PLs' EO**





Bruce  
McCarthy /LAKE/PPRD/ABB  
OTT  
02/14/2001 01:48 PM

Michael K Blarnesen/LAKE/PPRD/ABBOTT@ABBOTT,  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT,  
To Kennan C Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Bryan F  
Cox/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T  
Matalonis/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject Re: Consideration of IV work with ABT-594

Mike-

Thanks for the info. I agree...let's discuss this at the meeting I scheduled on Tuesday 2/20, 11-12:30, in the Analgesia Conference Room to discuss this issue (haven't yet sent out the agenda...look for it soon!). My mistake not to have invited Bryan!

Bryan...can you attend the meeting (date and time above)? We will be discussing how to advance our scientific understanding about the tolerability issues for ABT-594 and back-up compounds for pain in the NNR pharmacology.

Bruce.

Michael K Blarnesen



Michael K Blarnesen

02/14/2001 12:00 PM

To: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Bruce  
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Bryan F  
Cox/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Consideration of IV work with ABT-594

During our project review with Jeff Leiden there was a suggestion made that we consider performing intravenous phase I experiment(s) to better understand the issues associated with slow onset of action and also Adverse Events (nausea, vomiting, etc.) In previous team meetings, I recalled that there were some reservations expressed regarding the suitability of ABT-594 for IV administration (experimentally or commercially.) I discussed this with Kennan yesterday, and she provided some background for this concern, as follows:

- Her concern is with the NNR class, in general
- During IV administration of NNR molecules to non-anaesthetized dogs, gross increases in heart rate are seen almost immediately. This tendency was not able to be attenuated through reduction in administration rate, since the reaction occurs essentially when the first few drops of solution enter the blood stream.
- This response has not been observed during primate dosing
- Bryan Cox should have some data on CV profile dogs, most likely anaesthetized.


Chris / Bruce, let me know how you would like to proceed with this. Maybe a meeting with Kennan and Bryan would be a reasonable first step.

Mike B

CONFIDENTIAL  
ABBT0123130

P1. Exhibit 100 3/16/07 RM

**PLs' ES**

 Marilyn J  
Collicott / LAKE/PPRD/ABBO  
TT  
02/27/2001 10:12 AM  
To: sthenisult@rsi-nc.com  
cc  
bcc  
Subject: today's meeting

Hi Sheila

Attached are the handouts for todays meeting at 3:00 CST.



agenda.pub



Investigator tracking.xls



R-Team scheduling.xls



Subject-CRF Tracking.xls

Highly Confidential

ABBT238329

Thomas DEP. EX. NO. 26  
FOR ID., AS OF 4/13/07  
Bone

## M99-114 INVESTIGATOR LIST

Investigator Last Name	Inv. #	State	Coordinator	Phone #	Total Screened	Total Re-enrolled as of 11-4-07	Early Termination as of 02/20/07	Completed as of 02/20/07	CRFs In: House as of 2/27/07
Backonia	14272	WI	Christy Weaver	(808) 263-0170	4	3	1	2	3
Baumel (A)	7379	FL	Alfonso Moreno	(905) 865-0063	25	15	8	5	12
Baumel (B)	7379	FL	Jarella Cresto	(561) 368-1123					
Baton	7395	AR	Donna Hemphill	(501) 227-5051	15	7	1	6	5
Bromberg	15844	UT	Donna Baum	(801) 585-6051	26	14	6	8	13
DaBoid	15886	MN	Dane Whipple	(952) 993-2739	17	12	5	2	9
Druckman	15843	FL	SETH H. FORTNER	(727) 725-6131	7	6	5	1	6
Eisner	15890	FL	Maggie Szymczak	(954) 720-1899	17	6	4	2	5
Forde (f)	15842	NY	Michael Belotto	(516) 496-6506	3	2	1	1	1
Fried	12999	RI	Thomas Ricci	(401) 467-7760	15	9	4	1	8
Gibson	15841	AR	Kathy Belter	(501) 227-7499	26	16	6	12	18
Gibson	15840	NM	Randy Easley	(505) 262-7650	9	7	3	4	7
Haan	15833	MA	Debbie Davis	(617) 794-7232	8	5	4	2	6
Hewitt	14345	GA	Elen McKinzie	(404) 778-3176	12	8	5	3	7
Holmford	15838	NY	Maria Tassone	(718) 887-4793	11	5	3	2	5
Kelka, A	12497	PA	Donna Cole	(814) 693-4300	15	7	4	3	7
Klones	15002	TX	LEA PETER	(214) 315-5565	21	15	5	10	15
Kluby	9576	AZ	Burtonne Marshall	(623) 815-4713	20	10	7	2	10
Kluge (f)	13435	FL	Mathew Wink	(841) 836-1421	24	9	6	3	9
McGill (f)	15837	MO	Katherine Anderson	(314) 362-1404	17	8	2	5	5
Rowlandham	14348	CA	Jessica McCoy	(415) 865-7880	13	4	1	2	4
Shalbari	16334	TX	George Maroukan	(713) 795-0033 x26	48	18	9	9	16
Simmons	15836	PA	Kathleen Hay	(717) 531-8694	7	6	4	1	5
Singer	16230	FL	Mercy Navero	(954) 433-5785	30	15	7	8	10
Sivakumar	15835	AZ	Sandra Sowers	(602) 287-8025	14	9	4	5	9
Steel	15025	NC	MAURA STEEL	(252) 755-4848	10	8	6	2	8
Storey	14349	NY	Paula Levin	(518) 438-0922 press	21	15	6	3	8
Suri	16285	CA	Ruby Thussu	(559) 351-1881	4	3	3		3
Vink	15934	VA	Brenda Bailey	(757) 446-2973	15	6		6	6
Wormstein	13053	CA	John Newberg	(925) 390-7267	34	19	11	3	19
					505	269	192	170	234

Screen Failure Rate: 47%  
 Early Termination Rate: 49%  
 Completion Rate: 48%  
 Total Study Enrollment: 84%  
 CRFs In: 87%

All CRFs In

[FILE]

[PAGE]

[DATE][TIME]

Highly Confidential

ABBT238330

### Screen Tracking

Category	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	122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## M99-114 Early Terminations

Investigator	Subject #	Age	Days on Study Drug	Reason for Termination	Comments
Beckonja	4457	37	1	AE	urea nitrogen level high panic at 56
Baumel	4145	85	1	AE	nausea, etc.
	4146	78	10	AE	dizziness, weakness, heart palpitations, headaches, blurred vision
	4147	85	11	AE	dizziness, weakness, sweating, blurred vision, heartburn, headache
	4228	73	unk	AE	hypoglycemic episode
	4231	73	27	AE	hallucinations
Biton	4260	62			
Bromberg	4113	69	10	AE	nausea, etc.
	4115	45	5	AE	nausea, etc.
	4117	50	7	AE	nausea, etc.
	4118	49	10	AE	dizziness, vomiting, nausea
	4125	65	1	AE	extreme nausea
DeBord	4051	71	9	AE	nausea, etc.
	4053	52	49	SAE	diabetic ketoacidosis
	4055	75	15	AE	int. nausea/vomit since 8/1, int. abd bloating & constipation, decr. urine stream since 8/26
	4057	72	16	AE	intermittent nausea and vomiting
	4058		3	AE	dizziness, lethargy, vivid dreams, insomnia, increased neuropathic pain
	4060	57			
Drucker	4001	72	3.5	AE	joint pain in lower extremities
	4002	71	3	SAE	palpitations
	4003	78	0.5	AE	blurry vision
	4005	46			
	4006	72	1	AE	nightmares and intense neuropathic pain after 1st dose, whole body numb, wobbly, weak after 2nd dose
Eisner	4241	80	1	AE	nausea, etc. (went to ER)
Forde	4321	67	5	AE	disturbing dreams/anxiety
Fried	4083	66	14	SAE	syncopal episode related to historical atrial fib (admitted to hospital 5/30)
	4087	74	4	AE	diarrhea, GI upset, fatigue, light-headedness (patient took every dose following a meal)
	4089	81	6	AE	dizziness
Gibson	4354	73	1.5	AE	nausea
	4359	31	27	AE	nausea and vomiting
	4367	32	12	AE	nausea and vomiting
Gleason	4164	51	1	AE	dizziness, disorientation
	4165	51			
	4167	70			
Haag	4337	43	5.5	AE	dizziness ~2hrs post-dose x 10 episodes
	4340	72	5	AE	difficulty falling asleep, awakening more frequently
	4341	85	36	AE	mental status changes
Hewitt	4311	52	8	AE	nausea and vomiting
Holmlund	4193	53	7	AE/SAE	vomiting, fatigue/ broken pelvis
	4195	50	7	AE	nausea, vomiting
	4197	62	4	SAE	chest pain
Kafka	4417	74	6	AE	nausea, vomiting
	CMW		7	AE	jaw pain, insomnia, increased BP, heart palpitations, tingling
	4419	61	46	AE	nausea and vomiting
Kipnes	4065	64	3.5	AE	nausea
	4066	55	25	AE	nausea
	4070	48	10	SAE	left arm pain
	4072	70	7	AE	nausea, etc.
	4075	74	2	AE	severe nausea, shakiness
Kirby	4178	62	9	AE	backache
	4501	55	9	AE	unsteady gait, nausea, indigestion
Kluge	4131	70	8.5	AE	nausea, etc.
	4133	66	5.5	SAE	high blood glucose and chest pain due to GI problems (hospitalized 6/6-6/10)
McGill	4387	66	7	AE	nightmares, insomnia, nausea
	4390	59			
Shaibani	4450	58	30	AE	stomach ache
	4451	60	18	SAE	chest pain, shoulder pain
	4455	66	1	AE	got sick after first day
	4456	57	7	AE	headaches, lightheadedness, depression, rectal bleeding, sleeplessness caused by stomach acid

## M99-114 Early Terminations

	4462	55	10	AE	vomiting, stomach sickness, diarrhea, fluttering, moaning, crying, shaking, confusion
	4463	68	6	AE	depressing dreams, LOE
	4493	61	13	AE	nausea, diarrhea, vomiting, headache
Simmons	4273	58	11	AE	GI sx, cognitive dysfunction, unusual dreams, bad taste in mouth, headache, bodyache
	4275	69	10	AE	vomiting, nausea, headache, vivid dreams, diarrhea, chills
	4276	56	19	AE	nausea
	4277	56	9	AE	nausea, vivid dreams
Singer	4401	53		AE	angina secondary to coronary artery blockage
	4402	67	12	AE	dizziness, vomiting
	4403	57	25	AE	worsening insomnia
	4408	68	8	AE	vomiting
Sivakumar	4036	59	3.5	AE	nausea, etc.
	4040	57	7	AE	apprehensive, irritable, tinnitus, headache, burning eyes, diarrhea, vivid dreams
	4041	51	1	AE	nausea, vomiting, diarrhea
Steel	4209	69	22	AE	light-headed, dizzy
	4210	73	9	AE	vomiting
	4215	60	10	AE	severe nausea
	4216	52			
Storey	4098	70	6.5	AE	nausea, etc.
	4100	56	3	AE	nightmares
	4102	69			
Weinstein	4020	73			
	4021	65	13	AE	coughing, sore throat, cold sx (went to ER)
	4024	63			
	4489	79	6	AE	dizziness, nausea, diarrhea

	82	63.2	10.3		
Barnal	4227	57	unk.	Other	withdrew consent due to elective surgery
	4228	68	7	Other	withdrew consent
Brock-Sig	4129	65	0	Other	subject randomized prior to reviewing baseline diary, diary scores too low, subject never dosed
DeBord	4098	68	22	LOE	
Fried	4085	54	20	LOE	
Glavin	4055	64	20	Other	took anti-inflammatory due to hand pain
	4357	71	5	Other	had heels injected for pain
Heath	4305	60		Other	withdrew consent
Kirby	4179	49		Other	wanted to start narcotics for pain control
	4183	50		Other	history of alcoholism
Shaknel	4155	65	4	LOE	
Singer	4404	60	17	LOE	
	4405	64	20	Other	back spasms for knee pain
	4410		21	Other	moving out of state
Sivakumar	4038	50	27	Other	begun alternative therapy
Steel	4214	57	8	LOE	
Weinstein	4018	68		Other	withdrew consent
	4026	70	unk.	Other	lost to follow-up
	4030	73	19	LOE	
	4032	70	14	LOE	
	13	59.2			
TOTAL	95				

**PLs' EV**



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DISCOVERY

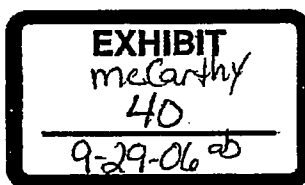
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Book #27  
Michael Meyer  
D-47W, AP9A-3



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Project Leader: Michael Meyer Chemistry: William Bunnelle Biology: Carol Surowy Commercial: Laura Robinson	<b>Neuronal Nicotinic Receptor Project:          ABT-594 Backup for Pain</b>
	DDC target date: 2Q01

## Objective

The primary objective of the Neuronal Nicotinic Receptor (NNR) project is to identify a structurally distinct follow-on to ABT-594 for use as a non-opioid, non-NSAID analgesic for the treatment of acute, chronic and neuropathic pain. The targeted compound should exhibit a comparable spectrum of analgesic activity to ABT-594 as assessed by existing preclinical models, and exhibit a minimum ten-fold, and ideally 30-fold improvement in therapeutic index with respect to emetic liability.

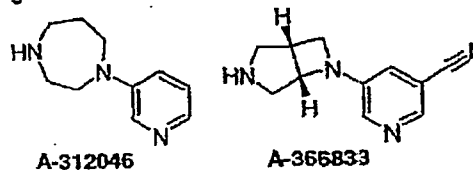
## Project Status Summary

During the past year, the project has continued to focus on a mechanism-based approach to the identification of compounds exhibiting retention of broad-spectrum analgesic activity associated with ABT-594, but with an improved therapeutic index relative to the key adverse events of emesis, nausea, and dizziness that have consistently been observed during the clinical evaluation of ABT-594. ABT-594 is currently completing a Phase IIb trial in diabetic neuropathy at doses up to four fold above the doses studied in the previous neuropathic pain trial, with results from that trial expected by May 2001. It will be critical to the continuation of the program to demonstrate enhanced clinical efficacy at these higher doses. Beyond this important milestone, the program is faced with two additional key issues: are efficacy and side effects governed by distinct and separable NNR subtypes, and can preclinical models accurately predict the improved therapeutic index required in an ABT-594 backup?

The preponderance of evidence continues to support the hypothesis that activation of  $\alpha 4$  subunit-containing NNR subtypes is required for analgesic efficacy, and that activation of  $\alpha 3$  subunit-containing NNRs is associated with emetic liability. Previously, detailed studies both within the project<sup>1</sup> and outside of Abbott<sup>2</sup> have provided convincing support for the role of central  $\alpha 4$  subunits in the mediation antinociception in models of acute thermal pain. Additional work within the last six months has extended these studies to models of persistent inflammatory and neuropathic pain. Whereas these studies have begun to implicate the involvement of peripheral sites as well as central sites of action, these studies continue to support the importance of  $\alpha 4$  subunit-containing NNRs from both the central and peripheral sites. Since the initiation of the NeuroSearch collaboration in January 2000, the project has screened all new and many historical compounds against human recombinant NNR subunit combinations. This data set has allowed further correlation of emetic liability to activation of the  $\alpha 3$  NNR subunit.

The project team has relied on the ferret emesis model to predict emetic and nausea liability, and general models of balance, coordination, and CNS-related toxicities as indicators of improvement in therapeutic index that may or may not correlate to the adverse event of dizziness reported for ABT-594. Using established models of efficacy, and these models of side effect liability, the project team has identified two compounds—A-312046 and A-366833—that exhibit a significantly improved therapeutic index across these models. The in vivo profile of A-312046 suggests particular utility in the treatment of neuropathic pain, but this compound suffers from poor bioavailability in two of three species examined. Transdermal and prodrug approaches are currently being explored. A-366833 exhibits efficacy across all pain models tested to date, has excellent bioavailability, and a 20 to 30-fold improvement in therapeutic index vs. ABT-594. Both A-312046 and A-366833 exhibit significantly improved selectivity for  $\alpha 4$ -containing NNR subtypes vs.  $\alpha 3$ , and both validate the viability of the molecular approach to the identification of follow-on compounds to ABT-594.

Figure 1. Structures of Best Leads



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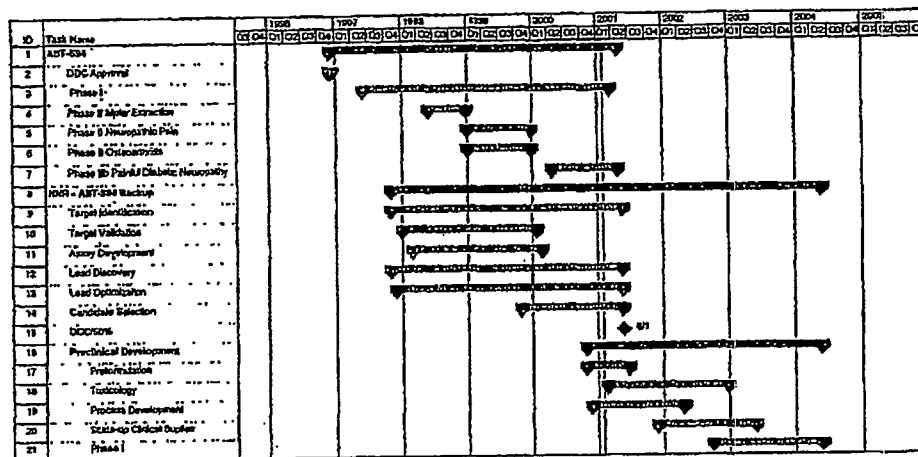
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1Q01

Discovery Project Review  
NNRs - ABT-594 Backup  
2

## Timelines



## SWOT Analysis:

### Strengths (technical and commercial factors)

- Novel mechanism and broad-spectrum of analgesic activity observed in preclinical models offers differentiation from other analgesics.
- ABT-594 has established proof of principle for both nociceptive and neuropathic pain states.
- Abbott has established a leadership position in the preclinical and clinical evaluation of NNRs for the treatment of pain.
- Abbott has established a six-year research collaboration with NeuroSearch (Denmark) that has provided access to several novel structural classes and has made available the human recombinant NNR subtypes as a screening tool.
- Efficacy in both nociceptive and neuropathic pain would differentiate compound from current therapies.
- Novel mechanism provides potential for use as monotherapy or in combination with an opioid or other MOI product (opioid-sparing regimens).
- Potential to complement oncology franchise as analgesic therapy for cancer pain.
- PPD building GP relationships in pain management with Mobic, and has strong relationships with Neurologists (neuropathic pain and migraine) through Depakote.

### Weaknesses (technical and commercial factors)

- Although newer compounds emerging from the project demonstrate comparable efficacy to ABT-594 with a decreased side effect liability as assessed in preclinical models, the degree to which these improvements will be realized clinically is unknown.
- The factors that prevent rapid absorption of ABT-594 in humans and thus limit the usefulness of ABT-594 for the treatment of acute pain have not been determined, and thus not resolved by potential backup compounds.
- The clinically relevant side effect of dizziness has no identified preclinical correlate, and cannot be directly addressed in the preclinical characterization of potential backup compounds.
- The correlation between in vitro profile and in vivo efficacy and safety profile is limited. Whereas lack of in vitro selectivity invariably translates into a poor therapeutic index, good selectivity does not guarantee an improved TI.

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1Q01

Discovery Project Review  
NNRs - ABBT-594 Backup  
3

#### Opportunities (commercial and competitive factors)

- Analgesia represents a very large market with significant unmet need, yet no novel class of analgesic exhibiting a new mechanism of action has emerged in the last fifty years.
- Need exists for agents with efficacy superior to COX-2s without the side-effect and dependence liability of opioids for treatment of nociceptive pain; opportunity is primarily in the oral segment.
- For neuropathic pain, need exists for oral therapies with superior pain relief, increased responder rates, and lower side-effects than the gold standard tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs).

#### Threats (commercial and competitive factors)

- Increasing competition from major pharmaceutical companies (e.g., SIBIA/Lilly, Aventis/Targacept, Novartis, Pharmacia, Johnson and Johnson); risk that another NNR may be first to market.
- COX-2s have raised the hurdle for treatment of chronic mild-moderate pain (especially OA and RA), and will dominate this market.
- Superior efficacy will be important to penetrate "moderate-severe" pain market.
- Pregabalin (currently Ph III) likely to have a neuropathic pain claim, and has the potential to raise the bar regarding efficacy and/or AE profile (Note: ongoing Ph III trials have very recently been halted due to toxicology finding in mice).
- Potential for negative public perception regarding nicotinic mechanism; public education and CME will be critical to lay the foundation for a successful launch

#### Market Overview

##### New or Target Specific Market Issues

Total worldwide sales of prescription analgesics in 2000 were approximately \$12.9 billion. NSAIDs represent the largest sales share by class, followed by non-narcotics, narcotics, and adjuvant analgesics (AEDs and TCAs). U.S. prescription pain sales were \$7.9 billion, an 18% growth over 1999, fueled by strong growth of Celebrex and Vioxx. In the US, COX-2s are replacing traditional prescription NSAIDs, and increasing the size of the Rx market due to switching from OTC products. Sales of the COX-2s grew from \$1.5B in 1999 to \$3.0B in 2000. The US neuropathic pain market is approximately \$500MM, and is driven by continued growth of off-label Neurontin usage in neuropathic pain (\$210MM in 1999 growing to \$350MM in 2000, factored for use in pain).

Ex-US prescription pain sales were approximately \$5.0 billion in 2000, with growth of 9% over 1999 sales. Ex-US uptake of the COX-2 inhibitors has been much slower, due to premium pricing vs. traditional NSAIDs, an average of one year launch delay vs. the US in major European markets, and no launch in Japan. However, EX-US sales of COX-2s has grown significantly, from \$100MM in 1999 to \$350MM in 2000. The ex-US neuropathic pain market is approximately \$300MM. Neurontin sales are only a fraction of US sales (estimate only \$60MM for usage in pain), with carbamazepine remaining the gold standard for neuropathic pain. Neurontin has not launched in Japan.

Growth of the neuropathic pain market will be driven by increasing prevalence of diabetes, and a growing elderly population will increase incidence of numerous disorders, including herpes zoster and stroke, which often lead to neuropathic pain. In addition, diagnosis is expected to increase as physicians and patients become better educated regarding neuropathic pain, and more effective and tolerable medications become available. The nociceptive pain market is also expected to grow due to increasing prevalence of OA and RA in an aging population and more aggressive usage of analgesics.

Significant unmet need remains in the treatment of both neuropathic and nociceptive pain (Figures 2 and 3). There are no highly efficacious treatments for neuropathic pain. A new agent that exhibited superior efficacy, even in the absence of an improved side effect profile, would constitute a therapeutic advancement. Although the nociceptive pain market is better served, only the opioids exhibit efficacy in the treatment of severe pain. An agent with the efficacy of an opioid with decreased side effect liability relative to an opioid would constitute a therapeutic advancement.

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NNRs – ABT-594 Backup  
4

Figure 2. Unmet Needs: Treatment of Neuropathic Pain

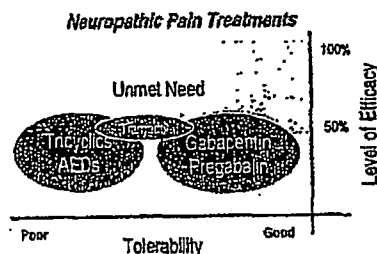
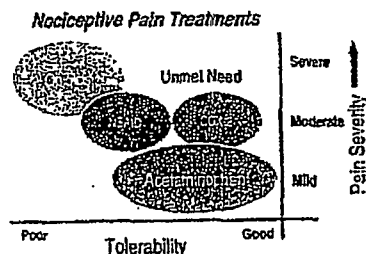


Figure 3. Unmet Needs: Treatment of Nociceptive Pain

**Target Product Profile**

Basis of Profile: Previous marketing research for ABT-594 PPCC, as well as follow-on qualitative and quantitative marketing research in analgesia.

Clinical Attributes/Probability	Preclinical Correlates
<ul style="list-style-type: none"> <li>Efficacy in neuropathic pain superior to gold standards (increase pain relief and/or increase responder rates)</li> <li>Efficacy in moderate to severe nociceptive pain</li> <li>Non-scheduled</li> <li>Onset of action within 30-45 minutes</li> <li>No tolerance, dependence or abuse potential</li> <li>Favorable safety profile</li> <li>Frequency of dosing no greater than BID</li> <li>No significant drug interactions</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy superior to gabapentin or pregabalin in Chung model of neuropathic pain</li> <li>Efficacy comparable to superior to NSAIDs in nociceptive pain models</li> <li>Lack of drug reinforcing properties</li> <li><math>T_{max} &lt; 30</math> min after oral administration in preclinical models</li> <li>Retains efficacy upon repeated administration, does not produce self administration in rodents</li> <li>Therapeutic index 10 to 30 fold greater than ABT-594</li> <li>Predicted human clearance comparable to or better than ABT-594</li> <li>Limited metabolism, clearance as parent drug</li> </ul>

**Development Challenges**

The emerging clinical profile of ABT-594 has significantly limited the potential market from the preclinical promise of efficacy in all pain states to a more limited scope of the treatment of neuropathic pain. Slow absorption and slow onset of analgesic effect plus significant adverse events of emesis, nausea, and dizziness have precluded ABT-594 from the large and lucrative acute pain and pain associated with osteoarthritis markets. There is, however, significant unmet need for the treatment of neuropathic pain; the existing drugs are minimally efficacious and the side effect profile is poor. In order to fully exploit the potential of the NNR pharmacology platform for the treatment of pain, compounds with significantly greater tolerability are required. The issue of rapid onset may not be an issue per se, but may only be an issue with ABT-594 as a result of being unable to dose at a sufficient level to achieve therapeutic plasma concentrations at early time points prior to  $t_{max}$ . The regulatory pathway for an indication in the treatment of neuropathic pain is much less well established than for the treatment of pain associated with osteoarthritis, and this will remain a development challenge for both ABT-594 and additional follow-on compounds.

The development paradigm adopted for ABT-594 needs to be challenged as backup compounds are brought forth for development. The assumption that solution dosing would provide a rapid answer as to the viability of NNR pharmacology for the treatment of pain resulted in incorrect conclusions as to the tolerability of ABT-594, and consequently resulted in a slowing down rather than an acceleration of the development program. Although third molar extraction was a logical starting point to evaluate ABT-594, this is a model that is optimized for evaluation of NSAIDs and not necessarily the most appropriate model for the evaluation of a novel pharmacology.

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5

## Scientific Logic for Drug Discovery

### Background

Although preclinical data from nicotine, and more recently from epibatidine, have been in existence for many years supporting the potential analgesic activity of NNR agonists, no clinical results unequivocally supporting a role for this novel pharmacology in the treatment of pain have emerged. ABT-594 has changed that situation. Clinical efficacy in trials of molar extraction, osteoarthritis, and neuropathic pain achieved with ABT-594 has validated the NNR approach to the treatment of pain, and Abbott alone is in possession of this information. ABT-594, however, is an imperfect drug. Effects were only modest at the maximum dose of 75 µg B.I.D., and the full potential of this pharmacology will be more clearly revealed when the results of the ongoing clinical trial in painful diabetic neuropathy (at doses of 150, 225, and 300 µg B.I.D.) become available. Dose-limiting side effects of emesis, nausea and dizziness have made it difficult to reach what we believe should be therapeutically relevant plasma concentrations of ABT-594 required to achieve maximal efficacy. Hence, the challenge facing the project team is to maintain the broad-spectrum analgesic efficacy of ABT-594 across models of acute, persistent and neuropathic pain while decreasing side effect liability, particularly in models of emesis.

### Drug Target

Previously, the project team and outside investigators have provided strong evidence for the involvement of the  $\alpha 4$  and  $\beta 2$  NNR subtypes in the mediation of nociception in models of acute thermal pain<sup>1-4</sup>. Both  $\alpha 4^{+}$  and  $\beta 2^{+}$  knockout studies, as well as antisense studies have strongly implicated the  $\alpha 4\beta 2$  NNR subtype in the modulation of acute antinociception. More recently, the project team has begun investigation of the differences and similarities between NNR mechanisms in acute models vs. mechanisms in models of persistent inflammatory and neuropathic pain. These ongoing studies confirm the involvement of supraspinal sites and the activation of descending inhibitory pathways, but also now implicate additional peripheral sites of action. In particular, in the Chung neuropathic pain models, sites within the vicinity of the dorsal root ganglia (DRG) cell bodies have been implicated as an important peripheral site of action for NNRs. Preliminary results suggest the involvement of the  $\alpha 4\beta 2$  subtype at these sites as well. Access to human recombinant NNR clones through the NeuroSearch agreement has made it possible to further refine the relationship between activity at the  $\alpha 3\beta 4$  NNR subtype and emesis liability. These results continue to support a clear link between activity at this subtype and emetic liability (see Progress to Date).

### Genomic Profile

There is a growing body of evidence to suggest genetically mediated differences both in the perception of pain and the effects of analgesics in the treatment of pain<sup>5,6</sup>. Mogil (Univ. of Ill.) has reported studies on the genetic variability across inbred strains of mice both to pain perception and the effects of various analgesics in numerous pain models<sup>7-10</sup>. Flores (Univ. of Texas) has recently demonstrated significant variability of NNR-mediated antinociception across various mouse strains<sup>11</sup>. In several instances, human disease states have been linked to genetic abnormalities of NNR subunits. Mutations of the  $\alpha 4$  subunit have been linked to autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)<sup>12-14</sup>, and mutations of the  $\alpha 7$  subunit have been linked to auditory gating deficits among schizophrenics and their immediate relatives<sup>15,16</sup>.

### Uncertainties, Assumptions and Hurdles

- It has been assumed that the modest efficacy observed to date clinically with ABT-594 is a result of under-dosing, and this assumption is supported by an analysis of plasma levels achieved clinically relative to plasma levels required to produce efficacy in preclinical models. The ongoing Phase IIb trial in painful diabetic neuropathy will resolve this uncertainty.
- The degree to which preclinical models can predict adverse event liability associated with ABT-594 and resulting follow-on compounds is limited. Whereas the ferret emesis model is a well-established and quantitative model, nausea can be judged only qualitatively and no validated models of dizziness have been established. The project team has operated on the premise that measurable effects on balance, coordination and muscle strength will be a suitable surrogate marker for clinical dizziness, an assumption that may or may not be true.
- The project team's approach to the identification of compounds with improved therapeutic index is based on optimization of selectivity for the  $\alpha 4$ -containing NNR subtypes in vitro. Although not all compounds that exhibit selectivity for the  $\alpha 4$ -containing subtypes exhibit efficacy with decreased emetic liability, it is certainly true that failure to achieve selectivity invariably results in compounds exhibiting no significant improvement in therapeutic index relative to ABT-594. At present,

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6

- there is no clear SAR pathway to compounds exhibiting complete specificity for the  $\alpha 4$ -containing NNR subtypes. In addition, there may be theoretical limits to the degree to which efficacy and side effect can be separated.
- The "ideal profile" required of an NNR modulator for the treatment of pain remains uncertain. The identification of compounds like A-366833 (see Properties of Lead Compounds) challenges the conventional wisdom that only compounds exhibiting full agonist activity (as measured by FLIPR assays) would be fully efficacious in pain models.

#### Abbott Insights and Competencies

Abbott is currently an industry leader in the field of nicotinic receptor research. Specifics of this competitive advantage include:

- Clinical proof of principle for the treatment of pain.
- Established collaboration with NeuroSearch, offering a significant expansion of the compound library and an opportunity to resume screening against human recombinant NNR subtypes.
- State-of-the-art behavioral models for assessing analgesic potential of preclinical leads.
- Large library of potent NNR agonists exhibiting potent analgesic activity.
- Collaborations and relationships with key opinion leaders in pain as well as NNR biology and chemistry.

#### Key Factors for Success with Milestones

##### Achieved

- Established screening facility in Norway; stable cell lines expressing functional  $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 4\beta 4$ , and  $\alpha 3\beta 2$  NNR subtypes; generating data on all new project compounds (3Q/00).
- Identified lead series, including novel series of fused diazabicycloheptanes, exhibiting a 20 to 100 fold better separation between  $\alpha 4\beta 2$  and  $\alpha 3\beta 4$  subtypes than that seen with ABT-594 (4Q/00).
- Further established the link between efficacy at the  $\alpha 4\beta 2$  subtype and analgesic effect (4Q/00).
- Extended initial finding relating to the importance of the  $\alpha 4\beta 2$  subtype in acute thermal pain to additional models of nociceptive and neuropathic pain (4Q/00).

##### Not achieved

- Presentation of DDC backup candidate to ABT-594 (4Q/00).

##### 0-6 months

- Complete safety evaluation of A-366833 for DDC presentation (2Q/01).
- Complete evaluation of efficacy and emetic liability upon oral administration of A-366833 (1Q0/01).
- Identify produg analog of A-312046 that produces a 3-5 fold improvement in oral bioavailability in the dog (2Q/01).

##### 6-12 months

- Address the limitations of ABT-594 for the treatment of acute moderate to moderately severe pain (4Q/01).

#### Criteria for Termination with Milestones

Termination of the cholinergic channel approach for the treatment of pain would be subject to the following:

##### 0-12 months

- No improvement in efficacy at doses of 300  $\mu$ g BID in diabetic neuropathy trial vs. initial 75  $\mu$ g BID trial (2Q/01)
- Mechanism based tolerance is observed clinically following higher doses (2Q/00)
- Inability to identify compound with comparable T.I. to A-366833 meeting all safety requirements for DDC approval (4Q/01).

##### 1+ year

- Physical dependence is observed clinically

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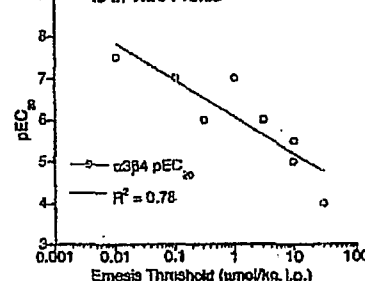
## Progress to Date

### Biological Advances

#### Correlation of Analgesic Efficacy or Emesis to NNR Subtypes

A strategy to use correlation to in vitro profile to identify NNR agonists that demonstrate analgesic activity with significantly reduced side effects has been pursued to identify a backup for ABT-594. The approach is based on our research, as well as that of others, which has revealed that activation of  $\alpha 4$ -containing, particularly  $\alpha 4\beta 2$ , NNR subtypes play a significant role in the antinociceptive properties of nicotine and related compounds, whereas other subtypes, e.g.,  $\alpha 3\beta 4$  NNRs, have been linked to some of the adverse (e.g. gastrointestinal and cardiovascular) side effects of NNR agonists. More recently, identification of novel compounds with greater NNR subtype selectivity within the project has provided significant support for this argument. We have found that compounds that show good agonist activity at  $\alpha 4\beta 2$ , but poor or less activity at  $\alpha 3\beta 4$ , show good analgesia together with reduced emesis and/or toxic side effects. To account for partial agonist activity and differences in oral bioavailability, Figure 4 correlates emesis threshold to  $EC_{20}$  (concentration required to produce 20% of the maximal effect of nicotine) values in the  $\alpha 3\beta 4$  cell line. Emesis is highly correlated to activation of the  $\alpha 3\beta 4$  subtype. On the other hand, compounds that show poor potency at  $\alpha 4\beta 2$  receptors, but good potency at  $\alpha 3\beta 4$ , tend to show a greater trend toward toxic side effects or emesis and are significantly less effective or ineffective at producing antinociception or antiallodynia in models of persistent or neuropathic pain. Certain highly  $\alpha 3\beta 4$ -selective compounds (e.g. A-333060) lacking any significant activity at the  $\alpha 4$ -containing subtypes are in fact hyperalgesic. Importantly, these correlations traverse several different series of compounds developed within the project. As subtype selectivity is an important issue in the identification of potential drug candidates with NNR activity, the project is continuing to make efforts to refine and strengthen these findings as it moves forward in the pain area, as well as in other potential target areas.

Figure 4. Correlation of Emetic Liability to In Vitro Profile



#### Cloning and Expression of NNRs and Identification of Compounds with NNR Subtype Selectivity

The NeuroSearch collaboration has allowed the Project to use cell lines expressing several of the different human NNRs to screen compounds for activity and subtype selectivity using FLIPR technology, in a relatively high throughput format. Human cDNAs for  $\alpha 4$ ,  $\alpha 3$ ,  $\beta 2$  and  $\beta 4$  were cloned in Norway at NeuroSearch during the first half of last year. During the 3Q 2000 NeuroSearch developed stable human cell lines (in HEK 293) expressing  $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 4\beta 4$  and  $\alpha 3\beta 2$ . Over the last 6 - 8 months these cell lines have been used at NeuroSearch to successfully screen all new compounds synthesized for the pain program here at Abbott, within the Project, and at NeuroSearch. The result has been the identification of a number of novel subtype-selective agonists, including those in new series such as one of the Project's current leads compounds (discussed below). The screening effort has also allowed us to increase our understanding of the NNR subtype profile, including effects of selectivity, potency, and efficacy, which may contribute to antinociception or antiallodynia.

In-house cloning efforts have focused on ferret receptors for  $\alpha 4$ ,  $\alpha 3$ ,  $\beta 2$  and  $\beta 4$ . Cloning of these cDNAs, which show good homology with the human receptors, is essentially complete. Stable cell lines expressing specific subtypes have been or are currently being developed and selected. As recent studies in the field continue to demonstrate increasing complexity to NNRs, use of recombinant receptors expressed in stable cell lines, transient expression of altered forms of the receptors, and studies using expression of the different subtypes in *Xenopus oocytes* (ongoing), will permit advances in our understanding of the distinct properties of these receptors. Initially these studies will provide: (i) greater insight into the correlation between subtype selectivity and effects observed in the ferret emesis model, and (ii) further understanding of the pharmacological and molecular properties of different NNR subtypes.

#### Mechanistic Studies

Both preclinical and clinical research indicate that the mechanisms underlying such pain states as acute, persistent or neuropathic pain can be quite different. Previous research in our project focused on the neuronal pathways and receptor subtypes that underlie NNR agonist-induced antinociception in a model of acute thermal pain. These studies demonstrated that NNR agonist-induced antinociception to acute thermal pain is mediated solely in the CNS and that antinociception to acute

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NNRs - ABT-594 Backup  
8

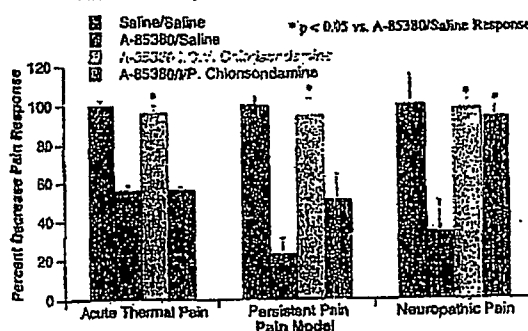
thermal pain occurs supraspinally. Use of selective receptor antagonists and antisense technology demonstrated the importance of the  $\alpha_2$  subunit in mediating NNR agonist-induced antinociception.

More recently we have examined the mechanism(s) of action in other pain states, i.e. persistent and neuropathic pain, in order to allow us to compare and contrast the manner through which NNR agonists are able to induce antinociception, analgesia and anti-allodynia. Due to its selectivity for NNR receptors, A-85380 was used as a prototypical agonist in these studies.

In order to examine the site(s) of NNR-mediated analgesic action in persistent pain, the ability of the NNR receptor antagonist chlorisondamine, a quaternary amine that does not cross the blood brain barrier, to alter A-85380-induced analgesia in the formalin model was assessed following systemic and central administration of the antagonist, which would induce peripheral and central blockade of NNR receptors, respectively. Centrally administered chlorisondamine blocked the analgesia induced by A-85380, whereas peripherally administered chlorisondamine only partially reduced A-85380-mediated analgesia, thus indicating a central site of action of NNR agonists as the major site in reduction of persistent pain.

A similar set of studies was performed to determine whether the anti-allodynia induced by A-85380 in the spinal ligation model of neuropathic pain was mediated either in the CNS or the PNS. In contrast to the acute and persistent pain models, both systemically and centrally administered chlorisondamine completely blocked A-85380-induced anti-allodynia. These findings were confirmed with another quaternary antagonist, hexamethonium, and another NNR agonist, A-312046, thus ruling out the possibility of nonspecific effects. Moreover, chlorisondamine given systemically did not alter A-85380-mediated antinociception in an acute thermal pain model using neuropathic rats, strongly suggesting that the effect could not be accounted for by the antagonists crossing the blood-brain barrier through damage caused during the initial surgery to induce neuropathic pain. Thus both central and peripheral sites of action of NNR agonists appear to make major contributions to reducing neuropathic pain. Results from these series of experiments are summarized in Figure 5.

Figure 5. Effects of Central and Peripheral NNR Blockade in Models of Acute, Persistent and Neuropathic Pain



Studies to identify the location of NNR receptors underlying the peripheral site of anti-allodynic action have focused on the primary receptive field of the neuropathic pain, the plantar surface of the rat paw, and on the other major peripheral site, the dorsal root ganglia (DRG). A-85380-induced anti-allodynia was observed on injection into the primary receptive field, but showed greater potency upon injection into the contralateral paw, strongly suggesting a systemic effect. In contrast, A-85380 infused directly onto the DRG induced a dose-dependent anti-allodynia at doses that were ineffective when given systemically. The anti-allodynic effects of NNR agonists at the level of the DRG were replicated using epibatidine as the agonist, indicating that this effect is general to NNR agonists. Furthermore, the finding that nonspecific neuronal inhibition induced by infusing lidocaine directly onto the DRG did not induce anti-allodynia supported the selectivity of NNR action. In order to identify the NNR receptor subtype(s) that are mediating the anti-allodynic action of A-85380 in the DRG, the ability of pretreatment of the DRG with the nicotinic antagonists DHBE, MLA, hexamethonium or mecamylamine to alter A-85380-induced anti-allodynia following DRG infusion has been assessed using at least one dose of each antagonist thus far. At 5 nmol, only DHBE blocked A-85380 induced anti-allodynia whereas mecamylamine, hexamethonium and MLA had no significant effect. These results argue for a role for the  $\alpha_2\beta_2$  receptor subtype in mediating the peripheral action of A-85380 in reducing neuropathic pain. Further studies to confirm these novel findings are ongoing. The finding that a significant contribution to anti-allodynia/neuropathic pain by NNR agonists is made through a peripheral, as well as a central, site of action may suggest that good blood-brain barrier penetration need not be necessary for an NNR agonist to reduce neuropathic pain. A compound with this profile may offer an advantage by minimizing the potential of centrally mediated AEs such as dizziness, or possibly emesis.

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NNRs - ABT-594 Backup  
9

### Properties of Lead Compounds

Two compounds have emerged, A-312046 and A-366833, exhibiting pronounced improvements in therapeutic index relative to ABT-594 with retention of broad-spectrum analgesic efficacy across models of acute, persistent and neuropathic pain, and validate the concept that improved therapeutic index can be achieved via an enhancement in in vitro selectivity. A-312046, however, suffers from poor oral bioavailability in dog and monkey, and may require either a transdermal delivery or prodrug approach. A-366833 exhibits a further improvement over A-312046 relative to therapeutic index, achieves excellent oral bioavailability across three species, but preliminary cardiovascular evaluation has revealed a potential effects on QT interval prolongation.

#### In Vitro Profile:

In radioligand binding assays for the high-affinity nicotine-binding site from rat brain homogenate (predominantly  $\alpha 4 \beta 2$ ), A-312046 exhibited comparable affinity to ABT-594 (0.051 nM vs. 0.049 nM), while A-366833 exhibited significantly weaker affinity (3.12 nM). In CEREP screening assays, both compounds showed excellent selectivity for the nicotinic receptor.

In recombinant cell-based functional assays expressing the  $\alpha 4 \beta 2$ ,  $\alpha 3 \beta 2$ ,  $\alpha 3 \beta 4$ , and  $\alpha 4 \beta 4$  NNR subunit combinations, A-312046 exhibited approximately 4-fold weaker activity at  $\alpha 4$ -containing subtypes and 28-fold weaker activity at the  $\alpha 3 \beta 4$  subtype relative to ABT-594. Full, or nearly full agonist activity was retained across all subtypes. A-366833 exhibited a 100-300 fold weaker response (relative to ABT-594) at the  $\alpha 4$ -containing subtypes and maximal efficacy was less than 100%, but was nearly inactive at the  $\alpha 3 \beta 4$  subtype, exhibiting approximately 15% of the maximal efficacy of nicotine (See Table 1, Figure 7).

Figure 6. Structures of Best Leads

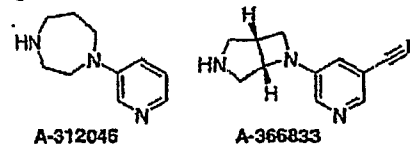


Table 1. In Vitro Profile of Most Promising Leads.

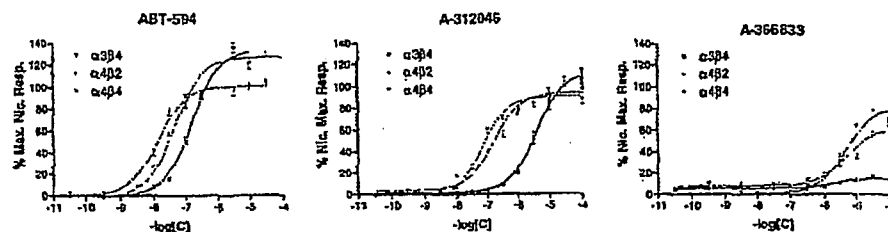
Compound	RLB* Ki, nM $\alpha 4 \beta 2$ (Rat Brain)	Functional Response (EC <sub>50</sub> , $\mu$ M, % of Maximal Nicotine Response in parentheses)					
		$\alpha 4 \beta 2$ (Clonal)*	$\alpha 3 \beta 2$ (Clonal)	$\alpha 3 \beta 4$ (Clonal)*	$\alpha 4 \beta 4$ (Clonal)*	$\alpha 4 \beta 2: \alpha 3 \beta 2$ 4 Sel. Ratio	$\alpha 4 \beta 4: \alpha 3 \beta 4$ Sel. Ratio
ABT-594	0.049	0.046 (127%)	2.69 (111%)	0.16 (134%)	0.014 (100%)	3.5	11
A-312046	0.051	0.16 (95%)	27.5 (60%)	4.10 (119%)	0.064 (82%)	28	64
A-366833	3.12	4.6 (83%)	N.D.	(16%)*	4.7 (83%)	NC*	NC*
Epibatidine	0.042	0.036 (139%)	0.076 (129%)	0.015 (97%)	0.0065 (108%)	0.4	2

\* RLB = radioligand binding

+ Data from side-by-side comparison using human cell lines (NeuroSearch, Norway)

\* EC<sub>50</sub> not reliably calculable (NC) for agonists with maximal response below 20%

Figure 7. In Vitro Dose-Response curves for functional response at NNR subtypes.



#### In vivo Efficacy Profile:

Both A-312046 and A-366833 exhibit approximately comparable efficacy to ABT-594 across models of nociceptive (persistent and acute), neuropathic and visceral pain. The differences in in vivo potency are commensurate with the differences in potency observed in vitro. The relative potency in models of nociceptive and neuropathic pain differ for A-312046 and A-366833, with A-

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10

312046 exhibiting its best potency and efficacy in the neuropathic pain model, whereas A-366833 is most potent and efficacious in the persistent nociceptive pain model (Formalin model). Both compounds exhibit the broad-spectrum profile of ABT-594 and morphine, whereas celecoxib (COX-2 inhibitor) and gabapentin show specificity for activity in models of inflammatory and neuropathic pain respectively. In the mouse abdominal constriction assay (ACA) model, a putative model of visceral pain, all three compounds exhibit full efficacy, with A-366833 being particularly potent in this model relative to its potency across the various rat models (Figure 10).

Table 2. In Vivo Efficacy Profile of Most Promising Leads.

Compound	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)	Writhing Pain (Mouse ACA)
ABT-594	+++ (0.08 $\mu\text{mol/kg}$ )	+++ (0.1 $\mu\text{mol/kg}$ )	+++ (0.03 $\mu\text{mol/kg}$ )	+++ (0.048 $\mu\text{mol/kg}$ )
A-312046	+++ (1.8 $\mu\text{mol/kg}$ )	+++ (0.7 $\mu\text{mol/kg}$ )	+++ (1.9 $\mu\text{mol/kg}$ )	+++ (0.3 $\mu\text{mol/kg}$ )
A-366833	+++ (3 $\mu\text{mol/kg}$ )	+++ (5 $\mu\text{mol/kg}$ )	++ (6 $\mu\text{mol/kg}$ )	+++ (0.11 $\mu\text{mol/kg}$ )
Celecoxib	++ (30 $\mu\text{mol/kg}$ )	++ (30 $\mu\text{mol/kg}$ )*	0	N.T.
Morphine	+++ (3 $\mu\text{mol/kg}$ )	+++ (10 $\mu\text{mol/kg}$ )	++ (3 $\mu\text{mol/kg}$ )	+++ (1.3 $\mu\text{mol/kg}$ )
Gabapentin	++ (300 $\mu\text{mol/kg}$ )	++ (100 $\mu\text{mol/kg}$ )	0	N.T.

+++ is >75% efficacy; ++ is 40-75% efficacy; + is 20-40% efficacy; 0 is no activity.

Values in parenthesis represent ED<sub>50</sub> values, all compounds administered i.p.

\* Minimal dose producing a statistically significant change from saline control.

N.T. = Not tested

Figure 8. Evaluation in Chung Model of Neuropathic Pain

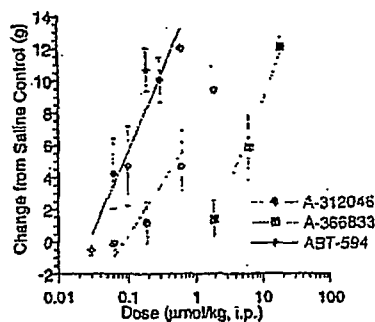


Figure 9. Evaluation in Formalin Model of Persistent Nociceptive Pain

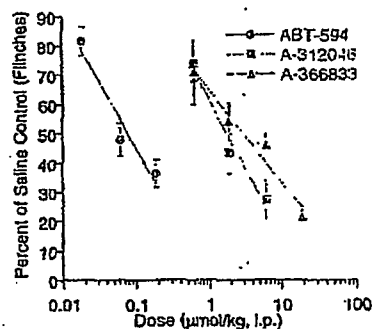
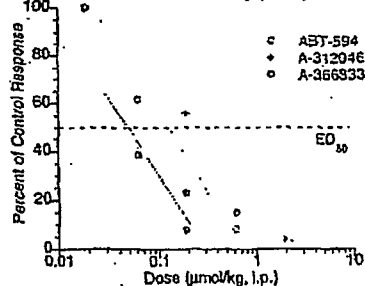


Figure 10. Mouse Abdominal Constriction Assay (ACA)

**GI Tolerability Profile:**

Nausea and emesis have been identified as significant adverse events clinically for ABT-594. The ferret emesis model has been used to quantify emesis in a preclinical model and evaluate the emetic potential of novel compounds. The no emesis threshold dose (highest dose to produce no emesis) for ABT-594, A-312046, and A-366833 was 0.01, 1.0, and 10  $\mu\text{mol/kg}$ , i.p., respectively. Thus, A-312046 and A-366833 exhibit approximately a 100-fold and 1000-fold shift in emetic liability relative to ABT-594.

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11**CNS Side Effect and Safety Profile:**

Within the therapeutic range, ABT-594 produces an array of qualitative effects on rodent behavior, including prostration, labored breathing, ataxia, head weaving, loss of motor coordination and increased urination. Beyond the therapeutic range, additional effects include seizures and deaths. Qualitatively, both A-312046 and A-366833 exhibit a pronounced lessening, or even absence of many of these observable changes within their therapeutic ranges. Certain of these effects, including motor coordination and balance (rat edge test), seizure threshold (mice), and ALD (mice) can be readily quantified (Table 3).

**Table 3. Safety profile of Best Leads.**

Model	ABT-594 ( $\mu\text{mol/kg}$ , i.p.)	A-312046 ( $\mu\text{mol/kg}$ , i.p.)	A-366833 ( $\mu\text{mol/kg}$ , i.p.)
Seizure Threshold (Mice, Approx $\text{ED}_{50}$ )	1.9	320	>400*
Approx. Lethal Dose (Mice, $\text{ED}_{50}$ )	19	300	>400*
Edge Test (Rats, $\text{ED}_{50}$ )	0.08	15	>19**

\* No deaths or seizures observed at highest dose (400  $\mu\text{mol/kg}$ ) tested.

\*\* Approx. 30% decrease in latency to fall at highest dose tested.

**Therapeutic Index Calculations:**

The ratio of effective dose in either the Chung model of neuropathic pain, the formalin model of persistent pain, or the mouse ACA model of visceral pain to the dose required to produce effects in various models of side effect liability can be used to calculate an approximate therapeutic index for ABT-594, A-312046, and A-366833 (Table 4). The values in boldface (Table 4) are where efficacy and side effect are measured in the same species by the same route of administration. A consistent pattern of improved therapeutic index is observed for both compounds independent of side effect model or efficacy model selected. Of particular importance to the clinically recognized dose-limiting side effect of emesis, A-312046 and A-366833 exhibit a 5- to 27-fold improvement in therapeutic index relative to ABT-594.

**Table 4. Therapeutic Index of Best Leads.**

Model	Ferret Emesis (No Effect Dose)	Rat Edge Test ( $\text{ED}_{50}$ )	Mouse Seizure Threshold ( $\text{ED}_{50}$ )	Mouse ALD ( $\text{ED}_{50}$ )
ABT-594 Chung ( $\text{ED}_{50}$ )	0.1	0.8	19	190
Formalin ( $\text{ED}_{50}$ )	0.12	1	24	240
Mouse ACA ( $\text{ED}_{50}$ )	0.21	1.7	40	400
A-312046 Chung ( $\text{ED}_{50}$ )	1.4	21	460	430
Formalin ( $\text{ED}_{50}$ )	0.56	10	215	200
Mouse ACA ( $\text{ED}_{50}$ )	3.3	50	1100	1000
A-366833 Chung ( $\text{ED}_{50}$ )	2	>12	>80	>80
Formalin ( $\text{ED}_{50}$ )	3.3	>18	>133	>133
Mouse ACA ( $\text{ED}_{50}$ )	90	>540	>3600	>3600

The clinical trial data with ABT-594 suggest that at least some level of efficacy is being observed at a dose (75  $\mu\text{g}$  bid) where emesis is minimal. Thus, the calculated T. I. from the preclinical models of 0.1 to 0.12 may represent a gross under-estimation of the tolerability of this compound. To better put into perspective the expected clinical therapeutic index of A-312046 and A-366833, the calculated improvements in therapeutic index (using the formalin and Chung efficacy models) relative to ABT-594 are presented in Table 5. Inclusion of data from the ACA model for A-312046 and A-366833 would yield T.I. improvements for emesis relative to ABT-594 of 16-fold and 430-fold respectively.

**Table 5. Relative Therapeutic Index Improvements vs. ABT-594 for Best Leads.**

Adverse Event	Therapeutic Index Improvement vs. ABT-594	
	A-312046	A-366833
Emesis (Ferret)	5-14x	20-27x
Seizure Threshold (Mouse)	4-11x	>11x
Edge Test (Rat)	10-24x	>15x

Analysis of therapeutic index based on peak plasma concentrations produces comparable values, with ABT-594 and A-312046 remaining relatively unchanged, and A-366833 producing a somewhat more favorable index (Table 6).

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12

Table 6. Therapeutic Index of Best Leads Based on Peak Plasma Concentrations.

	ABT-594	A-312046	A-366833
Peak Plasma concentration at ED <sub>50</sub> in Formalin Model (ng/ml)	2.6	43.7	108
Peak Plasma Concentration at Maximal Non-emetic Dose in Ferret (ng/ml)	0.46	26.5	1242
Therapeutic Index (Based on Peak Plasma Conc.)	0.17	0.61	11.5
Therapeutic Index (Based on Dose)	0.12	0.56	3.3

**Cardiovascular Safety Profile:**

A-312046 and A-366833 have undergone a preliminary evaluation in the canine Purkinje fiber repolarization assay. A-312046 produced no changes in action potential duration at 10 and 100-fold above therapeutic plasma concentration. A-366833 produced no significant effects at 10-fold above the therapeutic plasma concentration, but did produce an approximately 40% change in action potential at 100-fold above the therapeutic concentration. Both of these studies were performed in the absence of plasma. Correcting for plasma protein binding, the concentration intervals above therapeutic plasma concentration are approximately 20 and 200 fold.

A-366833 has undergone preliminary evaluation in the anesthetized dog preparation. A series of three thirty-minute infusions of A-366833 produced peak plasma concentrations of  $205 \pm 33$ ,  $851 \pm 124$ , and  $2512 \pm 646$  ng/ml (mean  $\pm$  SD) in the anesthetized dog. Preliminary analysis ( $n=4$ ) suggests plasma concentrations of A-366833 up to  $851 \pm 124$  ng/ml (8.5-fold therapeutic C<sub>max</sub>; rat formalin model, 12-fold above therapeutic plasma concentration at ED<sub>50</sub> in rat formalin model) exert no effect on QTc compared to vehicle treated controls. As plasma levels increased to  $2004 \pm 406$  and  $2512 \pm 646$  ng/ml, (20- to 25-fold of C<sub>max</sub>, 30 to 36-fold therapeutic at ED<sub>50</sub>) QTc increased  $23 \pm 10$  and  $30 \pm 8$  msec ( $n=4$ ; mean  $\pm$  sem) above pretreatment values, respectively, versus increases of  $14 \pm 3$  and  $16 \pm 3$  msec for vehicle controls ( $n=6$ ). Subsequently, at 30 and 60-minutes post infusion, QTc values were similar for drug and vehicle treated animals ( $944 \pm 167$  ng/ml). Although analysis of the full data set is incomplete, preliminary analysis suggests A-366833 produces a modest, dose-dependent increase in QTc. An unusually large difference in QTc interval between the saline control and drug groups at baseline (time = 0,  $\Delta$ QTc = 30 ms) was observed in this study. Plans are in place to add additional dogs to this study, and to complete the cardiovascular evaluation of A-312046.

The effects of A-366833 on other hemodynamic and cardiovascular parameters in the anesthetized dog were similar to those of ABT-594. In response to infusion of A-366833 mean arterial pressure was not affected by a plasma concentration of  $205 \pm 33$  ng/ml; mean arterial pressure decreased approximately 40 mmHg below baseline at the end of the second dose ( $851 \pm 124$  ng/ml), and remained at or near these levels during the high dose ( $2512 \pm 646$  ng/ml) and also during the 60-minute post-treatment period ( $944 \pm 167$  ng/ml). Heart rate and indices of cardiac contractile function increased modestly and transiently in response to A-366833; systemic vascular resistance decreased in a modest, dose-dependent manner. Pulmonary vascular resistance and cardiac output remained unchanged.

**Pharmacokinetics:**

The pharmacokinetic profile of A-312046 and A-366833 relative to ABT-594 in rat, dog, and monkey are outlined in Table 7. The poor oral bioavailability and high clearance rate of A-312046 and dog and monkey has prompted the evaluation of alternative routes of administration and/or prodrug approaches to the delivery of this compound. A-366833 exhibits excellent bioavailability across all three species. Metabolism studies are ongoing to enable prediction of human pharmacokinetic parameters.

Table 7. Pharmacokinetic Profile of Best Leads.

		t <sub>1/2</sub>	CLp	%F
ABT-594	Rat	1.5 h	1.7	61%
	Dog	4.7 h	0.4	35%
	Monkey	1.4 h	1.7	80%
A-312046	Rat	3.0 h	1.95	80%
	Dog	1.4 h	2.89	13%
	Monkey	1.5 h	2.36	3%
A-366833	Rat	1.5 h	3.02	73%
	Dog	2.6 h	0.35	109%
	Monkey	2.5 h	0.53	74%

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13

#### Compound-Related Issues:

A composition of matter patent application explicating claiming A-312046 was filed on Oct. 27, 1997 (by NeuroSearch), the U.S. application was filed on 10/27/98, and the World application published six months after that filing. The world application filing would be described as broad by Abbott standards. The Abbott-NeuroSearch research collaboration gives exclusive rights to the development of A-312046 to Abbott. A-366833 is described in an April 2000 U.S. filing, with a C.I.P. and world application to follow in April of this year. No publication has occurred nor have any office actions been received.

A-312046 is prepared in a single step from two readily available and inexpensive chemicals. Cost of goods have not been calculated but are expected to be inconsequential. A-366833 was originally prepared via a 21-step synthesis in enantiomerically pure form. Process research (D-45L) has begun process improvement within the last two months, and the synthesis currently stands at 16 steps.

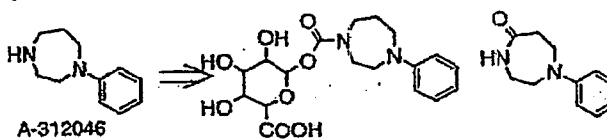
#### Medicinal Chemistry Advances

##### SAR Leading to A-312046:

Extensive SAR studies in the homopiperazine series have confirmed that substituents on the pyridine have powerful effects on subtype selectivity and *in vivo* activity. Small substituents at the pyridine 5-position that contain heteroatoms or  $\pi$ -systems often enhance selectivity for  $\alpha 4\beta 2$ -containing subtypes. For example, hydroxyl, carboxamide, ethynyl, cyano, and azido groups all lead to improved selectivity at the  $\alpha 4\beta 2$  receptor vs. the  $\alpha 3\beta 4$  subtype. The selectivity is often at the expense of overall potency and efficacy, but activity at  $\alpha 3$ -containing receptors is attenuated to a greater extent than that at  $\alpha 4$  subtypes. The range of useful substituents is limited, because bulkier groups cause loss of agonist activity for all subtypes. Other limits pertain to *in vivo* potency. Polar substituents, such as the hydroxyl group, tend to partition to the CNS poorly and have in general failed to exhibit broad-spectrum analgesic efficiency. Conversely, incorporation of a halogen (Br or Cl) at the 6-position increases potency for both *in vitro* and *in vivo* assays, but with concomitant loss of subtype selectivity and increased side effect liability.

A-312046 was selected as an optimized candidate from a series for structurally related homopiperazine analogs based on *in vitro* separation between activity at the  $\alpha 4\beta 2$  and  $\alpha 3\beta 4$  receptor subtypes coupled with excellent efficacy across pain models and enhanced separation between efficacy and emetic liability relative to ABT-594. A-312046 exhibited excellent oral bioavailability and long half life in the rat ( $F=80\%$ ,  $t_{1/2}=3$  h), but failed to provide acceptable oral bioavailability in either the dog or monkey (13% and 3% oral bioavailability respectively). GI absorption studies in the dog using radiolabelled A-312046 demonstrated >95% absorption, and subsequent studies (both *in vivo* and *in vitro*) implicated rapid first-pass metabolism. Two major metabolites were identified, both involving metabolism of the basic nitrogen (Figure 11). Consequently, it was reasoned that delivery of A-312046 to the general circulation, bypassing the gut, may be a viable approach to improving the pharmacokinetic shortcomings of this molecule. Two alternate strategies for delivery of 312046 are currently being assessed. The first involves evaluation of a transdermal (patch) dosing of A-312046. The physical properties of this compound (low MW, highly soluble, nicotine-like) are conducive to transdermal delivery. A theoretical estimate for the permeability of A-312046 through human skin has been established (D4P7), which predicts that it will be feasible to deliver up to 30 mg/day. Based on extrapolation of clinical doses of ABT-594, an efficacious dose of A-312046 is likely to be well within this amount. Moreover, a patch formulation may have advantages over oral administration in that local effects in the gut that may contribute to emesis are avoided, and transdermal delivery may allow more sustained plasma levels while blunting the rise to  $C_{max}$ .

Figure 11. Metabolism of A-312046



The second strategy would deliver A-312046 via a prodrug derivative that can be administered orally. For oral administration, the prodrug should be well absorbed and protected from the first-pass metabolism that depletes A-312046. The primary site of metabolism for A-312046 (oxidation, glucuronidation) is the basic nitrogen on the homopiperazine. Carbonyl derivatives at this site are not subject to these processes. For example, the p-aminophenyl carbamate of A-312046 (A-345151) is well-absorbed following oral administration in dog, and achieves high plasma levels. Unfortunately, the compound converts very slowly to A-312046 in plasma, precluding accumulation of therapeutic levels of the active compound. To date, more than 70 potential prodrugs of A-312046 have been screened (D4EK) for their ability to convert to A-312046 during 2h incubation in dog or human plasma. Simple amides and carbamates do not convert to A-312046 under these conditions. On the other hand, a set of carbamates designed for 'cascade' cleavage with a remote ester or anilide trigger, effectively deliver A-312046 in plasma. For

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NNRs - ABT-594 Backup  
14

one of these, A-367032, oral administration in dog provides plasma levels of A-312046 nearly twice as high as direct dosing of the parent, but only very small amounts of the prodrug are detected. The pharmacokinetic profile suggests effective delivery of A-312046 over the first two hours until prodrug is depleted, at which time the circulating levels of A-312046 begin to drop rapidly. The acetate trigger may be too sensitive, and it appears that the prodrug is substantially hydrolyzed in the time frame required for absorption. More sterically encumbered esters have now been prepared (See Figure 14), and are currently being evaluated in vivo.

Figure 12. Pharmacokinetic Profile of A-345151

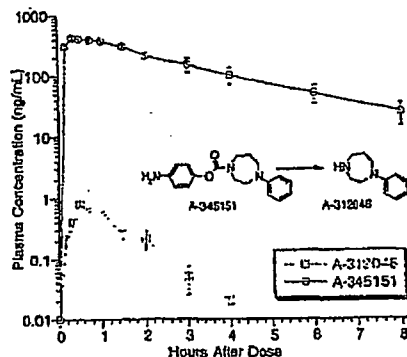


Figure 13. Pharmacokinetic Profile of A-367032

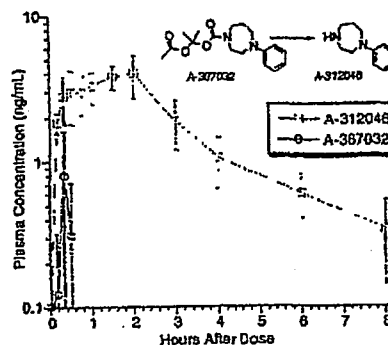
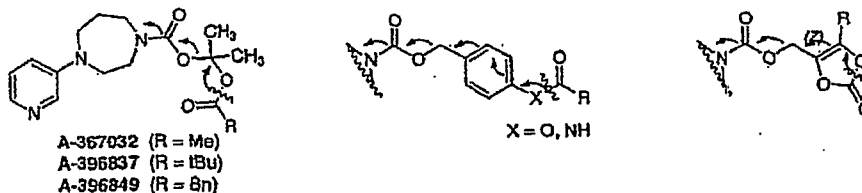


Figure 14. Cascade Prodrugs of A-312046

**SAR Leading to A-366833**

The SAR of the fused azetidine series exemplified by A-366833 is just beginning to emerge, and great sensitivity to structural changes is already evident. A-366833 is a partial agonist of modest potency at  $\alpha 4$  subtypes, but shows very little activity at the ganglionic ( $\alpha 3$ -containing) subtypes. In sharp contrast, the enantiomer A-365193 exhibits comparable partial efficacy and potency at both the ganglionic receptor and  $\alpha 4\beta 2$  subtype. This trend holds for some, but not all members of the series – the 6-Cl pyridine analogs are full agonists at all subtypes, with nearly indistinguishable profiles.

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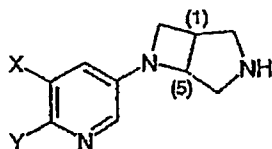
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NNRs - ABT-594 Backup  
15

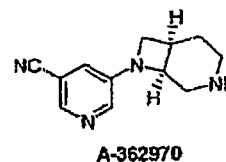
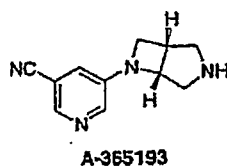
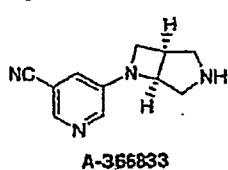
Table 8. SAR of 3,6-Diazabicyclo[3.2.0] Core.



A-Number	X	Y	Ring Stereochemistry	$\alpha 4\beta 2$ (EC50, %Max)	$\alpha 3\beta 4$ (EC50, % Max)
A-366833	CN	H	1R, 5S	4.6 $\mu$ M, 63%	16%
A-365193	CN	H	1S, 5R	9.3 $\mu$ M, 32%	19 $\mu$ M, 37%
A-366956	CN	Br	1R, 5S	0.32 $\mu$ M, 100%	2.1 $\mu$ M, 105%
A-361731	H	H	1R, 5S	2.2 $\mu$ M, 82%	30 $\mu$ M, 67%
A-361734	H	H	1S, 5R	2.3 $\mu$ M, 101%	32 $\mu$ M, 38%
A-361732	Br	H	1R, 5S	4.5 $\mu$ M, 33%	IA
A-365194	Br	H	1S, 5R	12 $\mu$ M, 16%	6.0 $\mu$ M, 29%
A-362124	H	Cl	1R, 5S	0.54 $\mu$ M, 133%	5.5 $\mu$ M, 145%
A-361733	H	Cl	1S, 5R	0.35 $\mu$ M, 118%	7.6 $\mu$ M, 83%
A-365191	Acetylenyl	H	1S, 5R	12 $\mu$ M, 39%	41 $\mu$ M, 27%
A-365192	Vinyl	H	1S, 5R	IA	IA

Placement of the pyridine on the other nitrogen of the bicyclic diamine leads to substantially more potent, but essentially non-selective compounds. So far, these have shown only weak activity in animal pain models. Expansion of the four-membered ring results in a sharp loss of potency, but the other ring accommodates this change - A-362970 has a very similar in vitro profile to A-366833. Scale up is currently in progress for in vivo evaluation.

Figure 15. Alternative Core Structures.

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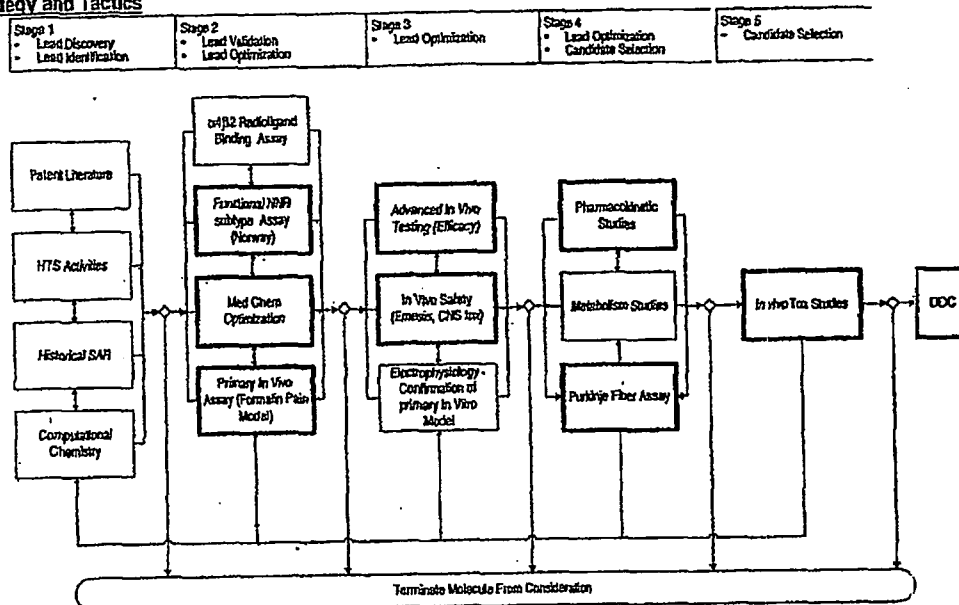
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16**Research Plan****Strategy and Tactics**

The current critical path activities are highlighted in heavy red lines, the lighter black lines indicate assay systems that are valuable in understanding overall compound profile, but are not normally criteria for dropping a compound from consideration. The majority (70%) of the NNR project activity currently focuses on medicinal chemistry optimization and in vivo screening. The critical path in vitro screening is conducted, in large part, by our NeuroSearch collaborators in Norway. The remaining effort (30%) is focused on in vitro method development and screening that are predominantly of relevance to the identification of NNR-subtype selective compounds for indications outside of analgesia.

**Biology and Pharmacology**

- Potency.** All compounds are initially evaluated for potency, as measured by the binding of [<sup>3</sup>H]-cytisine to  $\beta 2$ -containing NNRs (predominantly  $\alpha 4\beta 2$ ) in a rat brain homogenate. Throughput for complete concentration curves to generate  $K_i$  values is 24 compounds per week.
- Subtype Selectivity.** The functional activity of potent compounds ( $K_i < 100$  nM) at the  $\alpha 4\beta 2$ ,  $\alpha 4\beta 4$ ,  $\alpha 3\beta 4$ , and  $\alpha 3\beta 2$  NNR subtypes, as well as their agonist or antagonist properties, is determined through FLIPR methodology using recombinant human cell lines stably expressing these subtypes and the IMR 32 human cell line expressing native receptors, predominantly  $\alpha 3\beta 4$ . Throughput for complete dose response curves is approximately 12 compounds ( $n=4$ ) per week.
- Functional Activity: Behavioral Responses in Pain Models.** Several *in vivo* pain models are currently in use. These include rodent models that measure effects of compounds on acute, persistent, and neuropathic pain.
  - Acute Pain.** Rodent models for effects on acute pain include the mouse temperature, activity, analgesia (TAA) model (the TAA model assesses analgesic effects by hot plate methodology, as well as effects on temperature and activity), and the Hargreaves rat hot box model, both of which are currently used on a limited basis, when required for additional characterization of compounds. Throughput in these models is generally one compound (3 doses each) per week.
  - Persistent Pain.** Effects on persistent chemical pain are assessed using the rat formalin model. This model is used as the primary screen. Throughput in the formalin model is 3-4 compounds (3 doses each) per week.

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17

- c. Neuropathic Pain. Effects on neuropathic pain are assessed using the rat Chung model. Only selected compounds are evaluated in this model since it is highly labor intensive. This model requires ligation of the 5<sup>th</sup> and 6<sup>th</sup> lumbar nerves. After a two-week recovery period, a ½ day session is then required to obtain a full dose response for a single compound. Throughput is 3 compounds per week.
- d. Additional Behavioral Models. Several additional pain models are in place, including the mouse abdominal constriction assay for visceral pain; throughput in this assay, when required is one compound (three doses) per week.
4. Emetic, cardiovascular and other side effects. Emetic effects are evaluated in ferrets within the Project and also in collaboration with Integrative Pharmacology. Throughput in the ferret emesis model within the Project is 3 compounds (single dose) per week. For compounds of interest a complete dose response curve is generated. Selection of the dose for ferret emesis studies is initially based on the potency observed in i.p. dosing in the rat formalin model of persistent pain. Cardiovascular effects are evaluated in dogs, which appear to be the most sensitive species for NNR-mediated changes in blood pressure and heart rate. For compounds of particular interest, seizure threshold is assayed in mouse. Additionally, an attempt to measure dizziness is assayed using an edge test in rats and a rotarod test in mice. Throughput for these assays is generally one compound per week, when required.
5. Functional Activity: Neurotransmitter Release. Evaluation of the effect on neurotransmitter release provides a biochemical link between the direct effect of the compound on the NNR as measured in functional assays and the behavioral response in the *in vivo* pain models. *In vitro* neurotransmitter release assays are in place that measure the release of dopamine from either rat striatum or cortex, and the release of norepinephrine from either hippocampus or thalamus. For screening purposes, dopamine release in striatum and norepinephrine release in hippocampus are measured. Throughput for a 7 point dose response curve is 4 compounds (n=3) per week for each neurotransmitter. *In vitro* assays are also being developed to measure serotonin or GABA release from rat or mouse brain. In addition, procedures are in place for *in vivo* microdialysis of striatum, thalamus, hippocampus and spinal cord to measure the effects of compounds on the *in vivo* release of dopamine, norepinephrine, and serotonin.
6. Pharmacokinetics. In addition to characterization of potential lead compounds, pharmacokinetic analysis of representative subtype-selective compounds is necessary to enable proper interpretation of *in vivo* results from efficacy and side effect models. Typical studies on compounds of interest include detailed pharmacokinetic measurement of plasma concentrations of compound after i.v. or oral dosing, and also pharmacokinetic measurement of brain and plasma concentrations of compound after i.p. dosing in the rat. Throughput is one compound/week.

Electrophysiological assay. The Parallel Oocyte Electrophysiology Tester system (POETs), a throughput-enhanced electrophysiology instrumentation, has recently been developed and validated within the Project in collaboration with Automation Engineering. With the present system of six oocytes in parallel a significantly enhanced throughput over standard electrophysiological methodology, with assay of over 100 compounds per day (single concentration assayed in duplicate) is possible.

#### Medicinal Chemistry

Current work is directed toward expansion of the SAR around 366833. Planned analogs of 366833 have been chosen to provide the best chance for *in vivo* activity with overall selectivity. Pyridine substitutions include 5-ethynyl, cyano, methoxy, halo, azido, carboxamide, and methyl, with and without a 6-halogen in place. Reasonable quantities of both enantiomeric diamine cores are available to prepare this limited series. Likewise, the same derivatives are targeted for the homologous 3,8-diazabicyclo[4.2.0]octane series. Finally, N-alkyl derivatives of some of the very potent (and non-selective) 3-pyridinyl-3,6-diazabicyclo[3.2.0]heptanes will be evaluated. For the diamine series, like the pyridinyl ethers, N-alkylation causes a sharp attenuation in agonist activity that is more dramatic at the  $\alpha 3$  subtypes. The exceptional potency of the NH analogs suggests that N-alkyl versions may retain sufficient  $\alpha 4$  activity to be effective analgesics.

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18

Figure 16. SAR Plans for Diazabicyclo Core Structure.



## Competition

### Within Project Approach

Company	Compound	Indication	Status of compound	Status of project
<b>Nicotinics:</b>				
Eisai/Cyto-Med	(±)-Epibatidine analogs	Pain	Preclinical	Active
Taiho	GTS-21	Alzheimer's	Phase II	Seeking development partner
SIBIA Neuroscience (Rights to Lilly)	SIB-1508Y	Parkinson's Disease	Phase II	Discontinued
SIBIA Neuroscience (Rights to Lilly)	SIB-1553A	Alzheimer's	Phase II	Discontinued
SIBIA Neuroscience (Merck)	SIB-T1887	Pain	Preclinical	Unknown
Aventis/Targacept	RJR-2403	Alzheimer's	Phase I	Discontinued (PK issues)
Pharmacia	Unknown	Multiple	Preclinical	Active - focusing on α7
Pfizer	Cytisine analogs	Alzheimer's, pain	Phase I, compound unknown	Active
Astra Zeneca	AR-17779	Cognition, pain	Preclinical	Active - patent application on α7 selective compounds
Eli Lilly	Unknown	Multiple	Preclinical	Obtained exclusive license to human NNRs from SIBIA prior to acquisition of SIBIA by Merck
NeuroSearch	Multiple series	Pain, depression	Preclinical	Exclusive compound license to Abbott
NeuroSearch	NS-3573, 3956, 3939, 3890	Smoking cessation	Preclinical	Seeking licensing partner
Johnson and Johnson	Pyridyl ethers	Pain, Alzheimer's	Preclinical	Patent activity (NeuroSearch holds clear priority over published J&J patent)
Novo Nordisk		Alzheimer's	Preclinical	Patent activity
Univ. of Milan	DBO-83	Pain, Cognition	Preclinical	Collaboration with Abbott
<b>Muscarinics:</b>				
Lilly	LY-297802	Pain	Phase II (Discontinued)	Continued patent activity
Merck	L-689660	Alzheimer's, Pain	Preclinical	Unknown
Sanofi-Synthelabo	Pyridinyl diamines	Pain	Preclinical	Patent Activity

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19

Within Therapeutic Area – Focus on Neuropathic Pain

Product	Company	US Development Phase	Class/MOA	Comments
Pregabalin	Parke-Davis	III	Ca channel $\alpha 2\delta$ ?	Also for epilepsy, chronic pain – may be tox. issues affecting ongoing clinical trials
GV 196711	Glaxo	II	Glycine antagonist	Neuropathic pain and chronic pain
Memantine	Merz	II	NMDA antagonist	Dose ranging trial with 375 patients now underway
PN 401	ProNeuron	II	Unknown	For disease modification of PDN – pain and numbness next
Prosaptide	Myelos	II	Unknown	14 amino acid peptide Pain associated with nerve injury
Resiniferatoxin	Afferon	II	Vanilloid	Topical capsaicin analog
LTA	Astra	II	Sodium channel blocker	Topical w/ longer duration of action than capsaicin
CNS 5161	Cambridge Neuroscience	II	NMDA antagonist	Will not move to Ph II until a development partner is found

Competitive Analysis

Prescription analgesics to treat pain can be grouped into four classes; opioids, NSAIDs, other non-opioids and adjuvants. Opioids and combination agents are generally used to treat acute pain and cancer pain of moderate to severe intensity, but have AE and dependence liabilities. NSAIDs (including COX-2 inhibitors), have very good tolerability, but have only moderate efficacy and anti-inflammatory activity, and are used to treat pain of mild to moderate intensity. Tramadol is sometimes substituted for NSAIDs to treat chronic pain or pain of moderate intensity, but has much higher AE's than the NSAID class. Adjuvant analgesics are drugs such as tricyclic antidepressants and antiepileptic drugs have efficacy in the treatment of neuropathic pain, but offer only partial pain relief, have low (50%) responder rates, and undesirable AEs.

Pipeline compound Pregabalin, an anticonvulsant with MOA thought to be similar to conventional AEDs, may reach market well before the NNR compound. Recently identified toxicological issues from preclinical mouse studies have put the future of this compounds somewhat in doubt. Pregabalin is similar to Neurontin, but is more potent, has a wider therapeutic index and longer half-life, with potential for better efficacy and/or better side-effect profile than Neurontin. Generic Neurontin will also be available. However, unmet need is expected to remain high in neuropathic pain, since pregabalin will likely achieve only partial pain relief and low responder rates, as is found for other AEDs used in the treatment of neuropathic pain.

An NNR achieving the target profile outlined above would represent a breakthrough in treatment of moderate to severe pain, offering pain relief superior to NSAIDs without the AE liabilities of the opioids. The novel MOA of the NNR also offers potential for significantly improved pain relief and/or responder rates for neuropathic pain vs. gold standards. Numerous other companies are exploring NNR compounds and other MOAs that could also achieve the target profile. Entering the market after the competition, with a similar profile, would impact the commercial opportunity; however, the large market size, inter-patient variability regarding efficacy and tolerability of various agents, significant use of combination therapy, and high level of switching would likely make later entries viable, particularly if MOA remains a differentiating feature.

Competition within the NNR field is expanding rapidly. With the acquisition of SIBIA Neuroscience, Merck has become an important competitor. Lilly currently holds license to the SIBIA DNA patents, but rights are to revert to Merck at the end of this current licensing agreement. Pharmacia has had an active program for the past three years. Astra Zeneca, Pfizer, Targacept, and Johnson and Johnson all appear to remain active in this area.

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20**Project Resources****Project Team**

Individual	Expertise	Activities	% time
Carol Surowy	Bio GL	Coordination of in vitro and in vivo biology program	100
Clark Briggs	Electrophysiology	Identification of high affinity $\alpha\beta 2$ subform selective compounds; planning and setup of $\alpha 7$ program for schizophrenia	100
Dave McKenna	Electrophysiology	POETs screening, assay methods development	100
Pamela Puttfarcken	Pharmacology	Neurotransmitter release assays, methods development	100
Iris Jacobs	Pharmacology	Neurotransmitter release assays	100
Dave Anderson	Pharmacology	Radioligand binding assays, data analysis	100
Jerry Budzik	Pharmacology	5-HT <sub>2</sub> assay, nisoxetine binding assay development	100
Jeff Campbell	Pharmacology	In vitro functional screening, ferret emesis model	100
Rama Thirumapaya	Mol. Biology	Cloning and expression of ferret NNR subtypes, stable cell line development	100
Brent Putman	Mol. Biology	Cloning and expression of ferret NNR subtypes, stable cell line development	100
Lynne Ruefer	Behavior	Chung neuropathic pain model, mechanistic studies, development of anxiety and depression models	100
Kathy Kohlhaas	Behavior	Chung model, anxiety models	100
Pete Curzon	Behavior	Various pain models, development of schizophrenia models	100
Mike Buckley	Behavior	Pain models, antidepressant screening	100
Bill Bunnelle	Chem. GL	Coordination of chemistry program, patent preparation	100
Mick Dart	Med. Chem.	Prodrugs of A-312046	100
Arner Basha	Med. Chem.	Prodrugs of A-312046	100
Mike Schrimpf	Med. Chem.	A-366833 analogs, $\alpha 4$ -selective compounds	100
Jianguo Ji	Med. Chem.	A-366833 analogs	100
Jennifer Pace	Med. Chem.	Ring expanded 833 analogs, bridged analogs	100
Kevin Sippy	Med. Chem.	A-366833 analogs, $\alpha 4$ -selective compounds	100
Karin Tietje	Med. Chem.	Ring expanded analogs, bridged analogs	100
Keith Ryther	Med. Chem.	Prodrugs of A-312046	100

**Technology and Support Groups**

Group	Current FTEs	Priority (1-3)*	Milestone Date†	Description of Outcome Desired by Milestone Date
HTS Screening	0	2	9/01	Radioligand binding HTS against $\alpha 7$ receptor.
Automation Engineering	1	1	03/01	Development of HTS POETs, behavioral screening automation
Process Chemistry	4.5	1	3/01	Development of improved synthetic route to A-366833 and delivery of sufficient material for 2-week toxicology study in rats
PK and Metabolism	1	1	5/01	Evaluation of prodrug analogs of A-312046. Comparative assessment of metabolism profiles of ABT-594, A-312046, and A-366833. Evaluation of additional new lead structures
Toxicology	0	1	5/01	Two-week rat tox. studies on A-312046 and A-366833
Integrative Pharmacology	0.2	1	4/01	Cardiovascular evaluation of A-312046 and A-366833. Purkinje fiber assay of compounds related to A-312046 and A-366833 to evaluate SAR
Formulation	0.2	1	5/01	Solubility and stability assessment of A-312046 and A-366833
Total FTEs	6.9	* Priority: 1 = Must have, 2 = Should have, 3 = Nice to have † Avoid "ongoing". Provide specific dates to achieve milestone.		

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21External Resources

Organization	Activities
NeuroSearch: In vitro pharm.	5.6 Headcount: Cloning and expression of human NNR subtypes, development of stable cell lines, FLUPR screening of collaboration compounds, $\alpha 7$ radioligand binding assay
NeuroSearch: In vivo	2.7 Headcount: Evaluation of collaboration compounds in models of depression and anxiety.
NeuroSearch: Chemistry	2.7 Headcount: Synthesis of compounds for pain, depression and schizophrenia targets.

Adequacy and Optimization of Resources

Resources are adequate at this time for the identification of a follow-on to ABT-594 by 2Q/01. The project team is on track for establishing the identification of NNR modulators of the  $\alpha 7$  subtype as the next molecular target. The therapeutic indications for  $\alpha 7$  are most likely to include schizophrenia, and in particular the cognitive deficit aspects of schizophrenia.

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6668-R2

**PLs' EZ**



**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

Attendees:

Abbott:

J. Leiden, B. Dempsey, A. Higgins, D. Norbeck, J. Leonard, E. Ogunro, E. Sun, M. Verlinden, P. Nisen, R. Granneman, R. Patterson, E. Shek, X. Frapaise, J. Nemmers, J. Arnott, E. Fiorentino, R. Guillaume, D. Pizzuti, P. Scaman, M. Roebel, C. Ward, K. Hendricks, J. Tyree, Y. Fujiwara, T. Seely

Knoll/BASF pharma:

I. Loew, S. Roellinger, U. Granzer, N. Bender, B. Kamen, M. Spigelman, F. Frickel, F. Richter, S. Roellinger, T. Zimmerman, C. Mendel, E. Chong, Steven Fischkoff, M. Luz, T. Seaton, C. Parow, B. Barchuk, R. Nuber, T. Hirose, E. V. Borcke, B. Hargan, R. Krautheimer, U. Legler, R. Janocha, J. Salfeld, U. Grau

McKinsey:

J. Hopfield

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Wednesday, March 7**

7:30 am	Welcome/ introduction	10 min		J. Leiden
7:40 am	Meeting objectives	10 min		J. Leonard
	<b>Anti-Infectives</b>	<b>Presentation</b>	<b>Discussion</b>	
	Quinolones			
7:50 am	- ABT- 492	20 min	5 min	C. Craft
8:15 am	- HSR- 903	30 min	10 min	T. Hirose/R. Krautheimer
	<b>Anti-virals</b>			
8:55 am	Triangle projects	30 min	10 min	M. Heath-Chiozzi
	- HIV and HBV (FTC; DAPD)			
9:35 am	<del>Meeting</del>			
	<b>Urology</b>			
9:55 am	BSF 42027 (ETA/ BPH)	30 min	10 min	M. Luz/U. Legler
	<b>T3/T4</b>			
10:35 am	T3/T4	15 min	5 min	C. Schreiber/T. Miller
	<b>Asthma</b>			
10:55 am	Hokunalin tape	15 min	5 min	T. Hirose/R. Krautheimer
	<b>Oncology</b>			
11:15 am	ABT-510	20 min	15 min	P. Nisen
11:50 am	ABT-751	20 min	15 min	P. Nisen
12:25 pm	<del>Lunch</del>			
1:25 pm	ABT-518	15 min	5 min	P. Nisen
1:45 pm	Rubitecan	20 min	5 min	P. Nisen
2:10 pm	Theragyn	20 min	5 min	P. Nisen
2:35 pm	ABT-627	30 min	10 min	P. Nisen
3:15 pm	<del>Afternoon Break</del>			
	<b>Cardiology</b>			
3:35 pm	Darusentan (LU 135252) & other ETAs	30 min	10 min	M. Luz/M. Kirchengast
	<b>Thrombosis</b>			
4:15 pm	PEG-hirudin	30 min	10 min	V. Ifthekar/U. Legler
4:55 pm	Ancrod	30 min	10 min	D. Levy/U. Legler
5:35 pm	Urokinase/ Pro-urokinase	30 min	10 min	S. Guptha

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Thursday, March 8**

**Neuroscience**

		<b>Presentation</b>	<b>Discussion</b>	
7:30 am	ABT 594	30 min	10 min	B. McCarthy
8:10 am	ABT-963	15 min	15 min	Granneman/Doan/Bell
8:40 am	BSF 201640	30 min	10 min	B. Rendenbach-Mueller
9:20 am	BSF 74398 (Parkinson)	30 min	10 min	S. Dawe

10:00 am *Morning Break*

10:20 am	Dilaudid OROS	45 min	15 min	B. Gold/R. Krautheimer
11:20 am	BSF 190555 (Schizophrenia)	30 min	10 min	B. Rendenbach-Mueller

12:00 pm *Lunch*

1:00 pm	Hydrocodone	10 min	10 min	S. Collins
1:20 pm	Bimoclomol ( ABT-822)	30 min	10 min	B. Wallin

**Gastro-enterology**

2:00 pm	Ganaton (pro-kinetic)	15 min	5 min	S. Dawe/R. Krautheimer
2:20 pm	TU-199 (proton pump inh.)	30 min	10 min	T. Hirose/ R. Krautheimer
3:00 pm	AU - 224 (colon pro-kinetic)	20 min	5 min	T. Hirose/ R. Krautheimer

3:25 pm *Afternoon Break*

**Phase III Projects**

3:45 pm	ABT-773	30 min	15 min	C. Craft
4:30 pm	D2E7	45 min	30 min	C. Spiegler/.E. v. Borcke

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Friday, March 9**

**Phase III Projects (cont'd)**

		<b>Presentation</b>	<b>Discussion</b>	
7:30 am	Segard	45 min	15 min	L. Daum/T. King
8:30 am	J695	30 min	10 min	R. Janocha/T. King
9:10 am	Clivarine	30 min	15 min	F. Misselwitz/S. Schaeffer
9:55 am	<i>MingBak</i>			
10:15 am	Rythmol SR	30 min	15 min	A. Pethö-Schramm/E. Schneider
11:00 am	Levosimendan	30 min	15 min	C MacLeod

**Phase IV Projects**

11:45 am	Clarithromycin	15 min	5 min	C. Olson
12:05 pm	Omnicef	15 min	5 min	C. Olson
12:25 pm	<i>Lunh</i>			
1:25 pm	Kaletra	15 min	5 min	E. Sun
1:45 pm	Norvir	15 min	5 min	E. Sun
2:05 pm	Meridia ( Sibutramine )	15 min	5 min	E. Chong/W. Hargan
2:25 pm	Uprima	15 min	5 min	S. Bukofzer
2:45 pm	Trandolapril (patch, intervention trials)	15 min	5 min	B. Rendbach-Mueller/ U. Legler/N. Bender
3:05 pm	<i>AeronBak</i>			
3:25 pm	Fenofibrate	15 min	5 min	D. Yannicelli
3:45 pm	Depakote	15 min	5 min	K. Sommerville
4:05 pm	Gengraf	15 min	5 min	T. Japour
4:25 pm	<b>Conclusion</b>			Jeff Leiden

**PLs' FB**

Elizabeth  
Kowaluk/LAKE/PPRD/ABBOTT

03/08/2001 05:19 PM

Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT,  
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Bruce  
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K  
Biamesen/LAKE/PPRD/ABBOTT@ABBOTT, James  
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael D  
Meyer/LAKE/PPRD/ABBOTT@ABBOTT, James  
Steck/LAKE/PPRD/ABBOTT@ABBOTT, David C  
Ross/LAKE/PPRD/ABBOTT@ABBOTT, Nigel  
To Livesey/LAKE/AI/ABBOTT@ABBOTT, Laura  
Robinson/LAKE/AI/ABBOTT@ABBOTT, Howard S  
Cheskin/LAKE/PPRD/ABBOTT@ABBOTT, Walid  
Awni/LAKE/PPRD/ABBOTT@ABBOTT, David D  
Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W  
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Connie  
Faltynek/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep  
Dutta/LAKE/PPRD/ABBOTT@ABBOTT, Rosemarie K  
Waleska/LAKE/PPD/ABBOTT@ABBOTT  
John N Simons/LAKE/PPRD/ABBOTT@ABBOTT, Tim  
cc Vanbiesen/LAKE/PPRD/ABBOTT@ABBOTT, Steve C  
Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject ABT-594/Pain Strategy DSG - 3/5 Meeting Minutes

Thanks to all who attended last Monday's (3/5/01) meeting of the ABT-594/Pain DSG core team.

The meeting focused on summarizing key issues of concern for ABT-594, as a first step to framing and structuring the decision problem. The issues raised are summarized in the attached document. Please let me know if there is anything I have failed to capture, or if you have additional thoughts.

A number of issues were raised that apply more broadly to the subject of therapeutic area strategy, as well as specifically to ABT-594. These are collected at the end of the document in anticipation of future discussions - please note that this is not intended to be a comprehensive summary of issues related to pain strategy at this point.

At next week's meeting (Tuesday 3/13/01), we will review and discuss issues related to the NNR backups. As a starting point I will summarize those issues I have already become aware of through one-on-one discussions and background reading. I would also like to review a proposed approach to the development of a Pain Strategy at this meeting.



I look forward to seeing you next week. In the ABT-594-Pain DSG Core Team Minutes 3\_5\_01 meantime feel free to call (x84402) or e-mail with any comments or questions.

Liz

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Kowaluk DEP. EX. NO. 19  
FOR ID., AS OF 10/10/06  
GMS

ABBT298379

**ABT-594 / Pain Strategy Decision Analysis****Core Team Meeting – Minutes****Meeting Date:** 3/5/01**Attendees:**

Nigel Livesey	Mike Biarnesen	Liz Kowaluk
Laura Robinson	Rose Waleska	
Sandeep Dutta	Connie Faltynek	
Steve Townsend	Marleen Verlinden	
Bruce McCarthy	Mike Meyer	
Jim Sullivan	John Simons	

As a first step to establishing the frame for the analysis and structuring the decision problem, this core team meeting focused on identifying key issues specifically related to ABT-594.

The issues raised are summarized below under three broad subject headings:

- Can the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability, and how?
- What indications do we pursue for ABT-594, and how?
- What is the abuse liability and potential for scheduling of ABT-594?

In addition, several points were raised that are also of more general relevance to the broader subject of pain therapeutic area strategy. These are summarized at the end of this document.

**Can the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability, and how?**

**What is the therapeutic index that is consistent with regulatory and commercial viability? Does it differ for different pain states?**

- AEs observed include nausea, emesis, dizziness and vivid dreams (at high doses)

**Understanding the biological basis for the PK/PD issues and the prolonged  $T_{max}$  is important for optimization of ABT-594 itself, and for backups.**

**The following issues are relevant to understanding whether, how and to what extent the tolerability and therapeutic index can be improved:**

- Dose-response relationships for efficacy and AEs
  - o may differ for different pain states, amongst AEs, and for efficacy vs. AEs
- Pharmacokinetic/pharmacodynamic relationships for efficacy and AEs
  - o may differ for different pain states, amongst AEs, and for efficacy vs. AEs.
- Biological basis for efficacy and AEs?
  - o  $C_{max}$ ? Rate of rise of plasma levels? Receptor occupancy? Other?



- Rate of tolerance over time for efficacy and AEs:
  - may differ for different pain states, amongst AEs and for efficacy vs. AEs.
  - must confirm that efficacy does not wane over time (weeks-months) – tolerance.
  - using titration to improve tolerability is feasible if AEs, but not efficacy tolerate.
- Mechanism of action of ABT-594:
  - preclinical pharmacology is consistent with characterization of ABT-594 as nicotinic agonist.
  - analgesia mediated by NNRs – specific site of action is uncertain
  - nausea/vomiting mediated by NNRs, mechanism of action for dizziness uncertain.
  - smokers vs. non-smokers – no effect on efficacy, but differential tolerability – has implications for dosing and labeling; potential downside for marketing – must promote understanding of receptor diversity, broad family of receptors (ABT-594 vs. nicotine).
  - gender and strain differences seen in preclinical models – implications for humans, if any, are unknown.

Titration is under investigation as an approach to improve tolerability and therapeutic index

- Feasible if AEs, but not efficacy tolerate
- Effect of first dose – rate of rise
- Titrate over days to weeks – how can titration schedule be tailored to minimize AEs?
- Patient acceptance?
- May be commercially more acceptable in neuropathic pain – efficacy/tolerability trade-off differs
- Length of titration will be important.
- Is the decline in AEs sufficient to offset the impact of titration?
- ABT-594 would be vulnerable if a new competitor has no titration

Can alternative dosage forms and routes of administration provide a means of improving tolerability and therapeutic index?

- Enteric-coated PO formulation
  - raised as possibility but not discussed in detail
- Patch
  - may be advantageous if GI AEs are a result of direct, local action of ABT-594 on GIT.
  - decreases difference between peak/trough plasma level – may have implications for efficacy and AEs.
  - permeation data suggest feasibility
  - no formulation developed as yet (would be third party – implications for royalties/COGS)
  - ABT-594 is potent analgesic – lends itself to administration by patch.
  - longer formulation development than PO – PARD.
  - trend in pain treatment is to treat pain around the clock, rather than on a PRN basis – consistent with patch formulation (e.g. Knoll – hydromorphone OROS and others).
  - would restrict ABT-594 for use in chronic conditions.
  - have limited qualitative market research, more market research needed.
  - probably commercially acceptable, although PO dosage form preferred.
  - more suited to a "niche" market.
  - pricing and COGS may be an issue.
  - has potential impact on compliance for chronic conditions
  - concern that patch formulation may lead to perception that ABT-594 is a "strong" drug that should be reserved for severe, difficult-to-manage pain.
- Depot dosage form
  - injection/implantable (weeks to months duration of action) – cf. Lupron
  - chronic pain only

- o most useful for pain that is not variable
  - o formulation must be stable at 37°C
  - o never looked at – not currently under consideration.
- Sublingual/buccal:
  - o more suitable for acute pain
  - o impact on AEs uncertain - faster rate of rise of plasma levels may precipitate AEs if this is the underlying issue, or could potentially avoid GI AEs, if they are locally mediated.
- Parenteral:
  - o potentially useful to address issues surrounding PK/PD relationship
  - o potentially "completes" product line – start on i.v. in hospital, then convert to PO.
  - o separation of efficacy and AEs may be a particular problem with rapid rate of rise of plasma levels.
  - o AEs an issue in post-op setting, where patients experience nausea/emesis – is combination with anti-emetic feasible?
- Intrathecal:
  - o may be useful in anesthesiology – would be HPD
- Intranasal:
  - o not discussed.

#### GI absorption and $T_{max}$ issue

- Delayed onset of action precludes acute and general pain claims for ABT-594
- What is biological basis for the unexpectedly long  $T_{max}$  (4-5 hours after PO solid dosage form)?
- Liquid dosage forms have somewhat shorter  $T_{max}$  than solid dosage forms, but still longer than expected (and large variance).
- "White paper", summarizing current knowledge, is in preparation.
- Potential trade-offs associated with faster absorption and shorter  $T_{max}$ :
  - o increased probability of abuse liability
  - o faster onset of action,
  - o increased AEs, if AEs are related to rate of rise of plasma levels.

#### What indications do we pursue for ABT-594, and how?

##### Should our first entry be into neuropathic pain, as currently planned?

- There is no regulatory precedent for neuropathic pain – no drug has been approved for this indication, with the exception of Gabapentin in UK (but not an NCE). The most advanced compound, pregabalin, was recently withdrawn from clinical trials (carcinogenicity issues?).
- Relative unmet need in neuropathic pain, therefore regulatory agencies likely to be more open on the risk-benefit ratio issue. For this reason, entry to the market via a neuropathic pain indication is likely to be the preferred approach for ABT-594.
- In EU – role of the comparator is unclear (gabapentin ?, Tegretol in Germany?) – placebo preferred by Abbott.
- In neuropathic pain, tolerability versus efficacy trade-off may play out differently in US versus EU. The majority of US patients are on gabapentin. In EU, patients are not switching as readily to gabapentin (may be pricing issue), majority are on TCA and carbamazepine. This may translate to a lower efficacy vs. tolerability hurdle in EU.
- What is the positioning statement for ABT-594 in neuropathic pain?

- o best neuropathic pain drug because...
- o better than gabapentin (easier to use)
- o novel mechanism of action (non-opioid, non-NSAID).

How can we broaden the use of ABT-594 beyond neuropathic pain?

- Nociceptive pain?
- General pain claim?

How do we access the nociceptive pain market with ABT-594?

- Can we study OA patients who are not responding to NSAIDs/COX-2 and progressing to opioids (i.e. second-line treatment)? Many OA patients switch between medications.
- The above is analogous to the second step of the WHO analgesia ladder – cancer patients move relatively quickly to the second step.
- For cancer pain, ABT-594 could potentially be a molecule that has opioid-like efficacy, but is not scheduled.
- Low back pain would require long, large trials because it would be perceived that this is an entry to "general pain".
- In OA and low back pain, the comparison is likely to be to e.g. Vioxx – an outcome showing similar efficacy but higher AEs would not be advantageous.
- Current approach to nociceptive pain (OA) is a publication strategy - prefer indications to publication from commercial perspective.
- Barriers to entry are high (e.g. COX-2 inhibitors: 1.2 million details per year and 6000 reps.)

General pain claim not feasible for ABT-594, due to prolonged onset of action.

- Not a clear regulatory and clinical path – FDA is not necessarily accepting historical approach, wherein trials in OAVRA lead to a general pain claim. The general pain claim requires multiple models – not currently defined, but likely to include difficult to treat conditions like chronic low back pain and fibromyalgia.
- Both FDA and EU regulatory agencies leaning towards disease-specific claims – "you get what you study".
- First market entry with a general pain claim could force the compound to a lower price point, versus first entry into the neuropathic market – also more likely to get reimbursement entering into the latter market.

Is a "niche" product commercially attractive? What are the trade-offs for a "niche" compound vs. a "blockbuster" compound that is effective across a broad spectrum of pain states?

Chronic length of treatment is an issue from regulatory perspective:

- EU requires 6 months efficacy data and 1 year of safety data
- US requires 3 months of efficacy data for OA, information to be supplied for neuropathic pain – Jim Steck/David Ross.

Pricing strategy:

- Gabapentin priced at 4 times the price of COX-2 inhibitors – have they priced themselves out of the market?
- Should we price like COX-2 in EU?
- Price is considered less of an issue in US (premium pricing possible in neuropathic pain due to significant unmet need).

Combination products:

- Combinations of ABT-594 with COX-2/NSAID or opioid have been suggested in the past
- EU is moving away from approval of combination products.
- Not attractive as entry – co-prescribing is preferred approach.
- Would be most appropriately considered for compounds which act synergistically with ABT-594 (not additive – co-prescribe).

**What is the abuse liability and potential for scheduling?**

The regulatory and clinical path is known.

Scheduling is commercially detrimental.

"Nicotinic PR" is a potential issue - Abbott must be proactive to counteract.

**Issues of Relevance to Pain Therapeutic Area Strategy**

Many of the issues listed here also appear above, but are restated here for convenience in anticipation of later discussions.

- Pain states can be categorized as nociceptive (visceral or somatic) and neuropathic, acute vs. chronic, by severity, by disease state.
- Compare different strategies for playing in entire pain market - multiple entries ("niche" products) versus a single "universally effective" compound.
- For any given compound/mechanism of action, what pain states should be pursued and in what order?
  - Both FDA and EU regulatory agencies leaning towards disease-specific claims - "you get what you study".
- Neuropathic pain
  - Efficacy/tolerability trade-off differs in neuropathic pain compared to nociceptive pain; also differs in US vs. EU for neuropathic pain - has potential ramifications for regulatory approval and commercial viability.
  - No regulatory precedent for neuropathic pain - no drug has been approved for this indication.
  - Relative unmet need in neuropathic pain, therefore regulatory agencies likely to be more open on issues of risk-benefit ratio.
  - In EU, the role of the comparator is unclear for neuropathic pain (gabapentin, Tegretol?)
- How do we access nociceptive pain - OA (first or second line), cancer pain, low back pain, other?
  - Low back pain would require long, large trials because it would be perceived that this is an entry to "general pain".
  - In OA and low back pain, the comparison is likely to be to e.g. Vioxx - an outcome showing similar efficacy but higher AEs would not be advantageous.
- Should we pursue general pain?
  - Not a clear regulatory and clinical path - FDA is not necessarily accepting historical approach, wherein trials in OA/RA lead to a general pain claim. The general pain claim requires multiple models - not currently defined, but likely to include difficult to treat conditions like chronic low back pain and fibromyalgia.
  - First market entry with a general pain claim could force the compound to a lower price point, versus first entry into the neuropathic market - also more likely to get reimbursement entering into the latter market.
- Publications vs. indications?
  - Indications preferred from commercial perspective.

- Pricing strategy
  - Gabapentin priced at 4 times the price of COX-2 inhibitors – have they priced themselves out of the market?
  - Should we price like COX-2 in EU?
  - Price is considered less of an issue in US (premium pricing possible in neuropathic pain due to significant unmet need).
- Chronic length of treatment is an issue from regulatory perspective:
  - EU requires 6 months efficacy data and 1 year of safety data
  - US requires 3 months of efficacy data for OA, information to be supplied for neuropathic pain – Jim Steck/David Ross.
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- Combination products:
  - Combinations of ABT-594 with COX-2/NSAID or opioid have been suggested in the past
  - EU is moving away from approval of combination products.
  - Not attractive as entry – co-prescribing is preferred approach.
  - Would be most appropriately considered for compounds which act synergistically with ABT-594 (not additive – co-prescribe).

*ABT-594 Decision Analysis*

*Update: ABT-594 Intermediate Dose (75 – 125 mcg)  
Ph. IIb Study*

Pharmaceutical Executive  
Management Committee Review

October 8, 2001

*Decision Support Group*

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ABBT298404

*ABT-594 must deliver superior efficacy to gabapentin and low nausea/vomiting to result in significant "1<sup>st</sup> choice" physician usage.*

<u>Efficacy compared to Gabapentin:</u>		Inferior	Similar	Superior
<u>Nausea/Vomiting<sup>b</sup>:</u>				
Low		3 <sup>rd</sup>	1 <sup>st</sup> /2 <sup>nd</sup>	1 <sup>st</sup>
Moderate		None	2 <sup>nd</sup>	1 <sup>st</sup> /2 <sup>nd</sup>
High		None	3 <sup>rd</sup>	3 <sup>rd</sup>

<sup>b</sup> Nausea/vomiting:  
 Low: N<10%; V<5%  
 Moderate: N: 10-30%; V: 5-15%  
 High: N>30%; V>15%  
 Discontinuation rates due to AEs are assumed to be low, given that the clinical trial design provides an alternative to discontinuation by allowing for dose reduction if dose escalation is not tolerated.  
 Based on US and EU market research fielded 6/01.

- For use as "1<sup>st</sup>/2<sup>nd</sup>" or "2<sup>nd</sup> choice" of physicians, ABT-594 must deliver:
  - Superior efficacy to gabapentin with moderate nausea/vomiting; or,
  - Similar efficacy to gabapentin with low or moderate nausea/vomiting.
- Inferior efficacy to gabapentin and/or high nausea/vomiting and high discontinuation rates relegate ABT-594 to "3<sup>rd</sup> choice" or "would not prescribe".
- Global peak sales:
  - 1<sup>st</sup> choice: \$990MM
  - 1<sup>st</sup>/2<sup>nd</sup> choice: \$670MM
  - 2<sup>nd</sup> choice: \$500MM
  - 3<sup>rd</sup> choice: \$90MM

DSG: 10/8/01

2

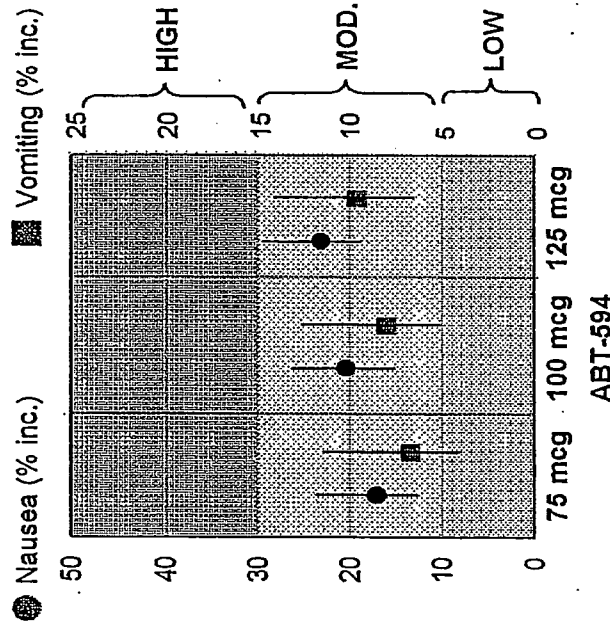
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ABBT298405



## *ABT-594 Intermediate Dose (75 – 125 mcg) Ph. IIb Study : Key technical assumptions.*

Statistical analyses predict a high likelihood that nausea/vomiting will fall in the "moderate" range at the doses to be studied in the Ph. IIb trial.



Symbols show predicted incidence of nausea or vomiting; lines show 95% confidence intervals.

DSG: 10/8/01

In the 75 – 125 mcg dose range, there is a good chance of demonstrating efficacy comparable to gabapentin, but little chance of demonstrating superiority.

### Current probability assumptions for Ph. IIb Efficacy:

ABT-594 superior to gabapentin: 0%

ABT-594 comparable to gabapentin: 80%

ABT-594 inferior to gabapentin: 20%

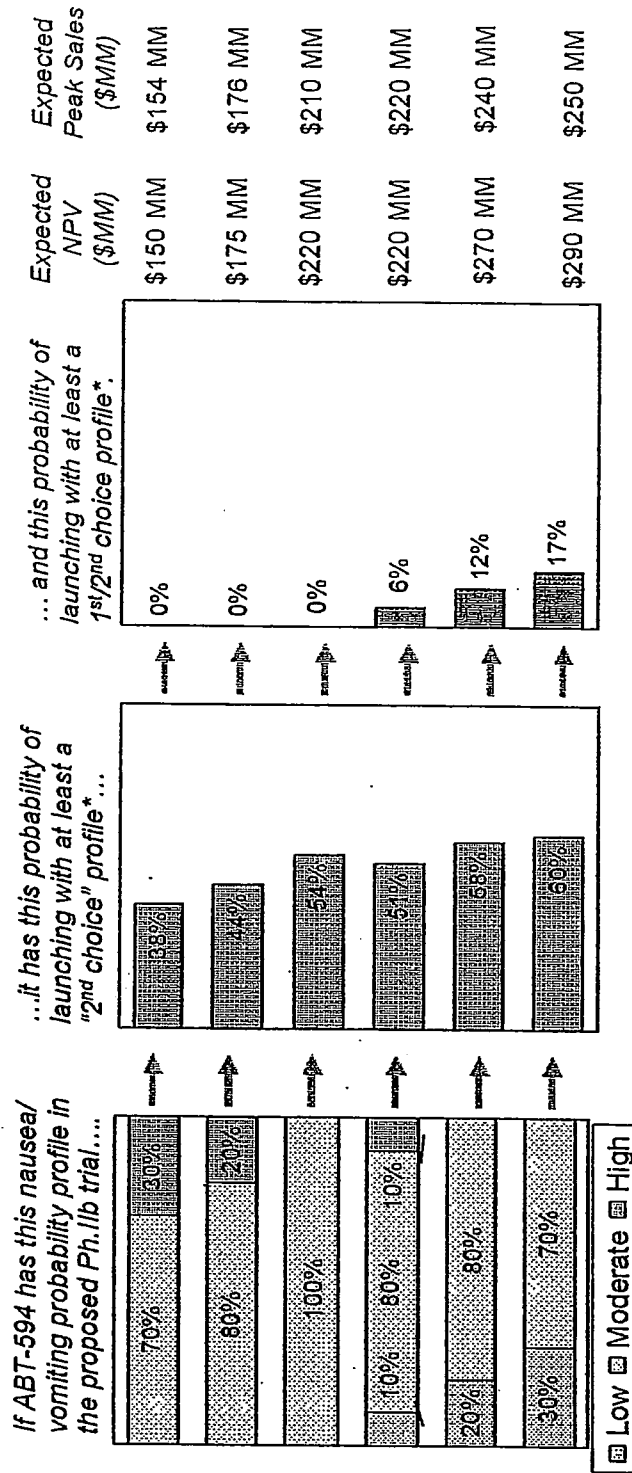
	Pain Reduction (%)
ABT-594:	
75 mcg*	38% (vs. 25% for PBO)
150 mcg (ITT)**	29% (vs. 17% for PBO)
150 mcg (completers)**	38% (vs. 18% for PBO)
Gabapentin:	39% (vs. 22% PBO)

\*Ph. IIa trial (diabetic neuropathic pain sub-analysis)

\*\* First Ph. IIb trial

*Assuming certainty of achieving "moderate" nausea/vomiting in Ph. IIb, ABT-594 has a 54% chance of launching with a "2nd choice" profile.*

- To have any chance of launching with a 1<sup>st</sup>/2<sup>nd</sup> choice profile, ABT-594 must have some probability of achieving "low" nausea/vomiting.



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ABBT298407

***BACKUPS***

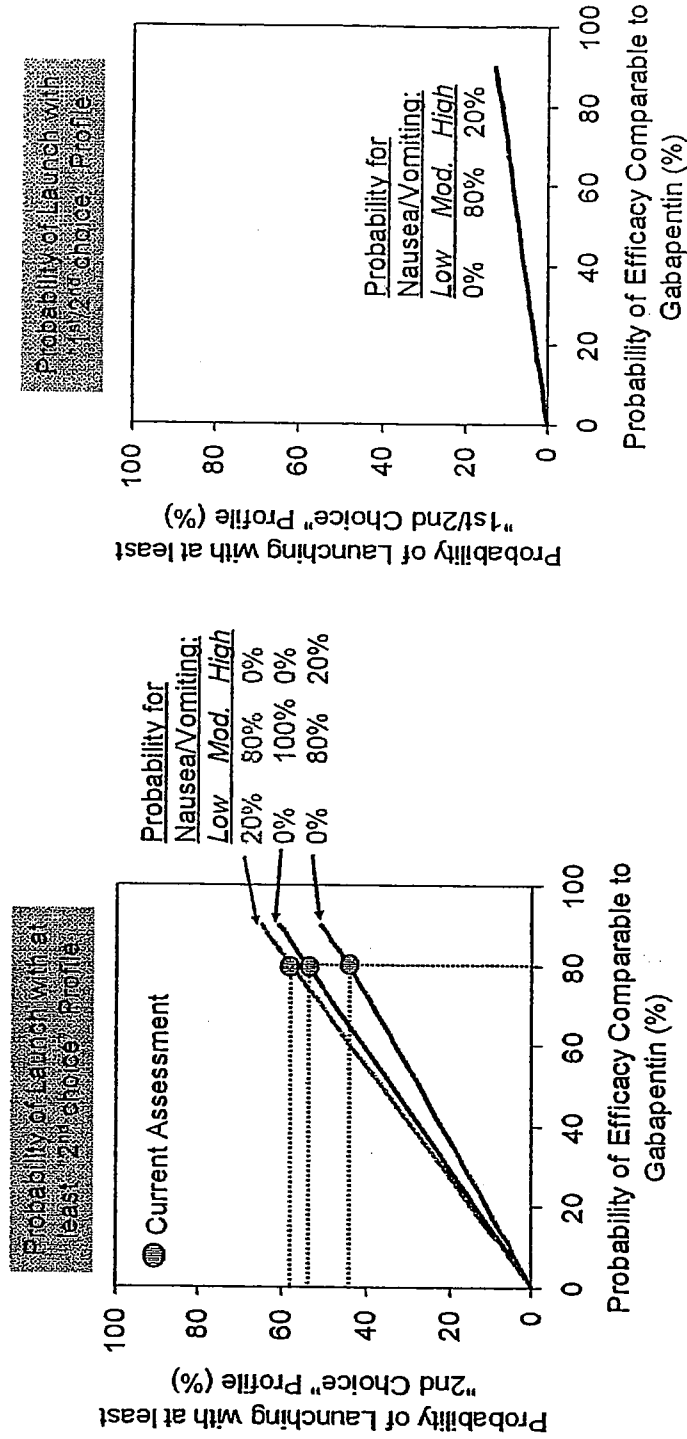
DSG: 10/8/01

5

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ABBT298408

*Sensitivity of Launch probability to the probability of achieving efficacy equivalent to Gabapentin.*



There is no chance of launching with a "1st/2nd choice" profile when there is no chance of low nausea/vomiting.

Industry average probability of launch for CNS drugs:  
 Entering Ph. II: 30%  
 Entering Ph. III: 52%

DSG: 10/8/01

6

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ABBT298409

## *Key market share and sales assumptions.*

- ABT-594 launch in 2006 with indication in diabetic neuropathic pain (head-to-head trial with gabapentin, and publication trial in chronic persistent pain (CPP)).
- ABT-594 base case 2010 share and sales (without anti-emetic):

Physician Usage	Share Neuropathic Pain (% Rx's)	Spillover Share CPP (% Rx's)	Global Sales (\$MM)
1 <sup>st</sup> choice	30%	2.5%	\$990
1 <sup>st</sup> /2 <sup>nd</sup> choice	20%	2%	\$670
2 <sup>nd</sup> choice	15%	1.5%	\$500
3 <sup>rd</sup> choice	3%	0%	\$90

} Assumed as "Success"

- Assumes 5% Rx growth and continuing trend for expansion of market for novel and premium-priced agents; one competitor (launch 2008-10) with profile similar to gabapentin: ABT-594 maintains TRx share if "1<sup>st</sup> or 1<sup>st</sup>/2<sup>nd</sup> choice"; 20% decline in share if "2<sup>nd</sup> choice".
- No share impact due to titration (7 – 24 days); 15% share loss with anti-emetic.
- 50% decline in share if ABT-594 is scheduled (P = 30%).
- Gabapentin: composition of matter patent to 2003; process patent to 2017.

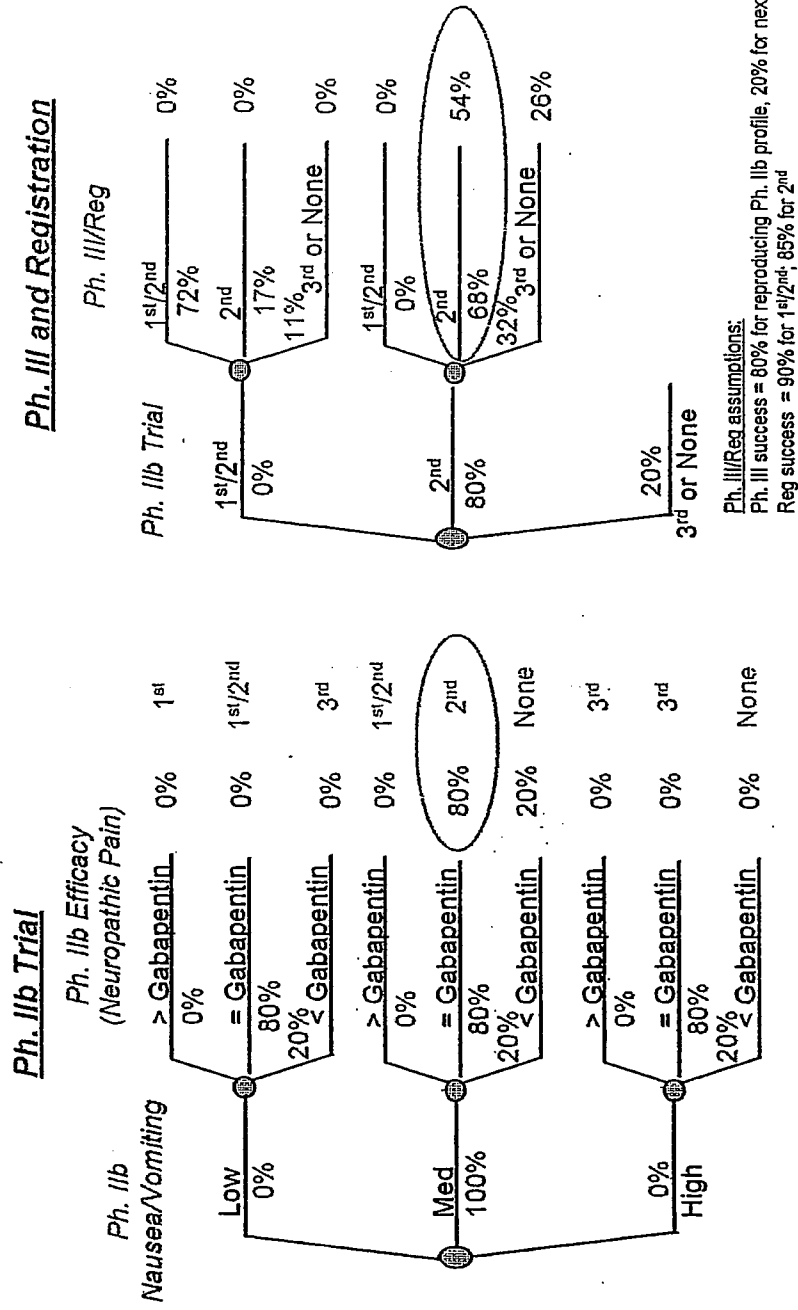
DSG: 10/8/01

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ABBT298410

## Base Probability Assumptions: Ph. IIb and Ph. III/Registration



DSC: 10/8/01

8

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ABBT298411

**PLs' FH**




Jessica Hopfield  
03/13/2001 07:22 PM

To: Patricia Weber/NJE/NorthAmerica/MCKINSEY@MCKINSEY  
cc:  
Subject: Please print and put in mail folder

----- Forwarded by Jessica Hopfield/NJE/NorthAmerica/MCKINSEY on 03/13/2001 07:23 PM -----

Michael Williams  
03/13/2001 04:10 PM

To: Jeff Leiden <jeff.leiden@Abbott.com>  
cc: Jessica Hopfield/NJE/NorthAmerica/MCKINSEY@MCKINSEY, Dick  
Ashley/CHI/NorthAmerica/MCKINSEY@MCKINSEY, David  
Keeling/CHI/NorthAmerica/MCKINSEY@MCKINSEY  
Subject: List of next steps from portfolio review 

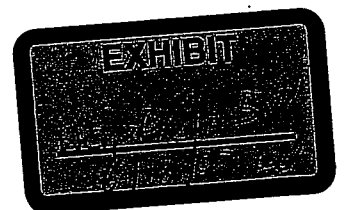
Jeff,

Please find attached a detailed list of the next steps by project, coming out of last week's development review. Where possible, we have assigned the responsibilities and timings we picked up during the discussions. You may wish to make changes to the list before it is more broadly distributed and we can make edits based on your handwritten comments if necessary.

We are also in the process of compiling the comments and results from the evaluation forms which we'll forward to you by later this week.



NEXT STEPS - development portfolio prioritization



# INITIAL PORTFOLIO PRIORITIZATION

Project	Priority	Next steps	Responsibility	Timing	C- continue P- pending T- terminate
<b>Anti-infectives</b>					
ABT-492	C	<ul style="list-style-type: none"> <li>• Address safety issues (including QTc) with internal/ expert review</li> <li>• Determine how many indications at launch (pay back)</li> </ul>	• J. Leonard	-	
HSR-903	T	<ul style="list-style-type: none"> <li>• Consider trading with Daiichi</li> <li>• Halt any new expenditure</li> </ul>	• J. Tyree	-	
ABT-773	C	<ul style="list-style-type: none"> <li>• Assess side effects issues with expert review (QTc and liver tox.)</li> <li>• Ensure all drug interactions are adequately covered</li> <li>• Assess relative to Ketek</li> </ul>	• J. Leonard • J. Leonard • I. Loew	-	
<b>Urology</b>					
BSF 420627	P	<ul style="list-style-type: none"> <li>• Set up task force to address issues and bring back plan to senior management               <ul style="list-style-type: none"> <li>- Reasons for failure of the SKB ETa/b antagonist</li> <li>- Design short (~4 week) PoP trial for symptom relief</li> <li>- Rationale for sustained release formulation</li> <li>- Nature of the Schwarz Pharma relationship</li> </ul> </li> </ul>	• J. Leonard	• By May	
<b>Hypothyroidism</b>					
T3/T4	P	<ul style="list-style-type: none"> <li>• Assess most appropriate ratio</li> <li>• Gain FDA feedback on study design</li> <li>• Determine ex-US market attractiveness (price)</li> </ul>	• J. Leonard	• By May	
<b>Asthma</b>					
Hokunalin tape	P	<ul style="list-style-type: none"> <li>• Conduct market research on acceptance by different patient segments</li> <li>• Determine how to position against long acting beta agonists and combination inhalers</li> <li>• Evaluate opportunity to gain complete access to the patch technology</li> </ul>	• A. Higgins/ E. Fiorentino  • J. Tyree	• May	

# INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

Project	Priority	Next steps	Responsibility	Timing
Oncology ABT-510	C	<ul style="list-style-type: none"> <li>Pursue proof of concept</li> <li>Leverage TAP knowledge of angiogenesis product development (appropriate endpoints)</li> </ul>	<ul style="list-style-type: none"> <li>Project team</li> </ul>	<ul style="list-style-type: none"> <li>As planned</li> </ul>
ABT-751	C	<ul style="list-style-type: none"> <li>Pursue proof of concept</li> <li>Use echocardiogram to monitor potential cardiotoxicity</li> <li>Resolve potent drug manufacturing approach</li> </ul>	<ul style="list-style-type: none"> <li>Project team</li> </ul>	<ul style="list-style-type: none"> <li>As planned</li> </ul>
ABT-518	Hold	<ul style="list-style-type: none"> <li>Wait for May results from Pfizer (will save ~\$1mill) and re-evaluate</li> <li>Halt all further expenditure</li> </ul>	<ul style="list-style-type: none"> <li>CMC group</li> <li>Senior management</li> </ul>	<ul style="list-style-type: none"> <li>May</li> </ul>
Rubitecan	P	<ul style="list-style-type: none"> <li>Significant clinical rework required (funded by partner)- further in-depth review required</li> <li>Make a proceed decision when 2Q data available</li> </ul>	<ul style="list-style-type: none"> <li>J. Leonard</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> </ul>
Theragyn	P	<ul style="list-style-type: none"> <li>Negative Initial scientific perspective - further in-depth review required, e.g.,               <ul style="list-style-type: none"> <li>Determine if there is a PoC to support claim</li> <li>Address GMP issues</li> <li>Determine best control to demonstrate efficacy</li> </ul> </li> <li>Re-look at partnership contract</li> </ul>	<ul style="list-style-type: none"> <li>J. Leonard</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> </ul>
ABT-627	C	<ul style="list-style-type: none"> <li>Seek alternative funding (e.g., NCI) before starting major trial</li> <li>If move ahead               <ul style="list-style-type: none"> <li>Determine how to ensure NDA filing in 2004</li> <li>Get FDA input since survival not primary endpoint</li> <li>Harmonize US and EU study design and inputs</li> </ul> </li> <li>Consider partnership (e.g., BI or established oncology player)</li> </ul>	<ul style="list-style-type: none"> <li>J. Tyree</li> <li>J. Leonard, P. Nisen</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> <li>ASAP</li> </ul>
			<ul style="list-style-type: none"> <li>J. Tyree</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> </ul>

# INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

Project	Priority	Next steps	Responsibility	Timing
Cardiology/ thrombosis				
Darusentan (LU 135252)	Hold	<ul style="list-style-type: none"> <li>Continue currently budgeted funding for next 6 months</li> <li>Do not start any new trials (e.g., hypertension planned for May)</li> <li>If proceed, plan for pilot to look at effects in sperm and tetragonectomy</li> <li>Consider out-license or swap</li> </ul>	<ul style="list-style-type: none"> <li>Project team</li> </ul>	<ul style="list-style-type: none"> <li>Ongoing</li> </ul>
LU 208075	Hold	<ul style="list-style-type: none"> <li>Continue currently budgeted funding for next six months</li> <li>Look at Myogen deal</li> <li>Out-license or swap</li> </ul>	<ul style="list-style-type: none"> <li>J. Tyree</li> </ul>	<ul style="list-style-type: none"> <li>ASAP</li> </ul>
Levosimendan	C	<ul style="list-style-type: none"> <li>Conduct detailed expert panel review for trial design</li> </ul>	<ul style="list-style-type: none"> <li>J. Leonard</li> </ul>	<ul style="list-style-type: none"> <li>May</li> </ul>
PEG-hirudin	P	<ul style="list-style-type: none"> <li>Set up expert panel for commercial assessment (is diabetes an option?)</li> </ul>	<ul style="list-style-type: none"> <li>E. Ogunro</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> </ul>
Ancrod	T	<ul style="list-style-type: none"> <li>Identify out-licensing opportunities</li> </ul>	<ul style="list-style-type: none"> <li>J. Tyree</li> </ul>	<ul style="list-style-type: none"> <li>TBD</li> </ul>
Urokinase	P	<ul style="list-style-type: none"> <li>Market research required on open cath</li> <li>Match versus tPA in dose-ranging studies to determine efficacy</li> </ul>	<ul style="list-style-type: none"> <li>E. Fiorentino</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> </ul>
Pro-urokinase	C	<ul style="list-style-type: none"> <li>Identify opportunities to speed up program</li> </ul>	<ul style="list-style-type: none"> <li>Project team</li> </ul>	<ul style="list-style-type: none"> <li>TBD</li> </ul>
Clivarine	C	<ul style="list-style-type: none"> <li>Assessment by HPD (review previous evaluation and new trial data)</li> <li>Understand finished product manufacturing cost</li> </ul>	<ul style="list-style-type: none"> <li>E. Ogunro</li> </ul>	<ul style="list-style-type: none"> <li>By May</li> </ul>
Rythmol SR	C	<ul style="list-style-type: none"> <li>Continue filing</li> <li>Verify if package is likely approvable</li> <li>Assess commercial attractiveness in a generic market</li> </ul>	<ul style="list-style-type: none"> <li>B. Dempsey</li> <li>Project team</li> </ul>	<ul style="list-style-type: none"> <li>Ongoing</li> </ul>

# INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue  
P- pending  
T- terminate

Project	Priority	Next steps	Responsibility	Timing
<b>Neuroscience</b>				
ABT 594	P	<ul style="list-style-type: none"> <li>• Await results from ongoing PII trial – probable T</li> <li>• Project team to develop decision criteria for go/no go</li> </ul>	<ul style="list-style-type: none"> <li>• Senior management</li> </ul>	<ul style="list-style-type: none"> <li>• June/July</li> </ul>
ABT 963	C	<ul style="list-style-type: none"> <li>• Identify a co-development/co-promotion partner (TAP high on list)</li> <li>• Evaluate benefits of the long half life in pain and cancer (including additional physician market research)</li> <li>• Explore cancer prophylaxis and Alzheimer's indications</li> </ul>	<ul style="list-style-type: none"> <li>• J. Tyree</li> <li>• Project team</li> </ul>	<ul style="list-style-type: none"> <li>• TBD</li> </ul>
BSF 201640	P	<ul style="list-style-type: none"> <li>• Complete review of all schizophrenia NCEs with expert panel</li> <li>• Complete staffing of internal project team, but halt further expenditure beyond looking at hepatic tox. and QTc</li> <li>• Understand Novartis contract and level of interest</li> </ul>	<ul style="list-style-type: none"> <li>• I. Loew</li> <li>• Project team</li> <li>• J. Tyree</li> </ul>	<ul style="list-style-type: none"> <li>• By May</li> </ul>
BSF 190555	P	<ul style="list-style-type: none"> <li>• Complete review as above</li> <li>• Halt further expenditure pending outcome</li> </ul>	<ul style="list-style-type: none"> <li>• I. Loew</li> </ul>	<ul style="list-style-type: none"> <li>• As above</li> </ul>
BSF 74398	C	<ul style="list-style-type: none"> <li>• Allow DevCo to continue development</li> <li>• Re-look at relationship with DevCo</li> </ul>	<ul style="list-style-type: none"> <li>• Project team</li> <li>• J. Tyree</li> </ul>	<ul style="list-style-type: none"> <li>• By May</li> </ul>
Diluadid Oros	Hold	<ul style="list-style-type: none"> <li>• Return to ALZA or out-license to other interested partner</li> </ul>	<ul style="list-style-type: none"> <li>• J. Tyree</li> </ul>	<ul style="list-style-type: none"> <li>• TBD</li> </ul>
Hydrocodone	C	<ul style="list-style-type: none"> <li>• Assess regulatory pathway</li> <li>• Understand DEA impact on manufacturing</li> </ul>	<ul style="list-style-type: none"> <li>• Project team</li> </ul>	<ul style="list-style-type: none"> <li>• By May</li> </ul>
Bimoclomol (ABT 822)	P	<ul style="list-style-type: none"> <li>• Await data from ongoing trial in April before deciding whether to continue - probable T</li> <li>• Halt further expenditure pending outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Senior management</li> </ul>	<ul style="list-style-type: none"> <li>• April</li> </ul>

**INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)**

C- continue  
P- pending  
T- terminate

Project	Priority	Next steps	Responsibility	Timing
<b>Gastro-enterology</b>				
Ganaton	P	<ul style="list-style-type: none"> <li>• Conduct U.S. commercial assessment with TAP</li> <li>• Assess how to position in Europe versus generics and implications for comparative trial</li> <li>• Develop model to assess spend at different termination points</li> </ul>	<ul style="list-style-type: none"> <li>• E. Fiorentino</li> </ul>	<ul style="list-style-type: none"> <li>• By June</li> </ul>
TU-199	T	<ul style="list-style-type: none"> <li>• Terminate outside Japan</li> </ul>	<ul style="list-style-type: none"> <li>• Bob Funck</li> </ul>	<ul style="list-style-type: none"> <li>• By May</li> </ul>
AU-224	C	<ul style="list-style-type: none"> <li>• Develop and pursue a small PoC trial in humans ASAP (consider niche indication first and leverage Marlene's expertise)</li> <li>• Conduct market research on IBS versus constipation (including pricing)</li> </ul>	<ul style="list-style-type: none"> <li>• Project team</li> <li>• Project team</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate</li> <li>• ASAP</li> </ul>
<b>Immunology</b>				
D2E7	C	<ul style="list-style-type: none"> <li>• Conduct intensive product review               <ul style="list-style-type: none"> <li>- 2 day meeting with J. Lennard's group (already in process)</li> <li>- ½ day session with senior management group</li> </ul> </li> <li>• Important actions include               <ul style="list-style-type: none"> <li>- Approach FDA for fast track and compassionate use</li> <li>- Develop strategy for DMARD claim in first submission</li> <li>- Assess need for Enbrel assay to detect HAHAs</li> <li>- Assess delivery device options</li> <li>- Evaluate additional indications (e.g., Psoriasis, Crohns, heart failure) and pediatric program</li> <li>- Profile Celltech product</li> <li>- Assess impact of additional IV program on reimbursement</li> </ul> </li> <li>• Develop list of potential marketing partners for quids</li> </ul>	<ul style="list-style-type: none"> <li>• J. Leonard</li> <li>• Various</li> </ul>	<ul style="list-style-type: none"> <li>• By May</li> <li>• By May</li> </ul>
			• J. Tyree	

# INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue  
P- pending  
T- terminate

Project	Priority	Next steps	Responsibility	Timing
Immunology (continued) Segard	Hold	<ul style="list-style-type: none"> <li>• Continue filing in EU and Canada</li> <li>• Put on hold in US – consider creating a small team in the US to analyse data, propose smaller PII study</li> <li>• Research pricing, marketing and Phase IV plans in Europe</li> <li>• Look at TNF-alpha levels retrospectively to see stratification with IL-6</li> <li>• Assess manufacturing strategy</li> <li>• Identify potential out-licensing opportunities (Genentech)</li> </ul>	<ul style="list-style-type: none"> <li>• Project team</li> <li>• J. Leonard</li> </ul>	<ul style="list-style-type: none"> <li>• Ongoing</li> </ul>
J695	P	<ul style="list-style-type: none"> <li>• Decide on most attractive indications from Abbott and partner perspective</li> <li>• Discuss with partner ways to share the various indications and potential for TNF-alpha combinations</li> <li>• Add commercial person to the project team by this week</li> </ul>	<ul style="list-style-type: none"> <li>• J. Tyree</li> <li>• E. Fiorentino</li> <li>• J. Tyree</li> <li>• Ongoing</li> </ul>	<ul style="list-style-type: none"> <li>• ASAP</li> </ul>



# INITIAL PORTFOLIO PRIORITIZATION (CONTINUED)

C- continue  
P- pending  
T- terminate

Project	Priority	Next steps	Responsibility	Timing
<b>PIV programs</b>				
Clarithromycin	C	• None identified	-	-
Omnicef	C	• Talk to partners	• J. Tyree	-
Kaletra	C	• None identified	-	-
Norvir	C	• None identified	-	-
Meridia	Hold	• Conduct commercial assessment for CNS and depression (P&L)	• B. Dempsey, J. Arnott, E. Fiorentino	• ASAP
		• Assess combination therapy with fibrates		
		• Assess outcomes trial design to meet preferred commercial profile; determine payback	• Project team	
Uprima	C	• Ensure no redundant trials with TAP in Europe	• Project team	• Ongoing
Trandolapril patch	T	• Halt all activities	• Project team	• Immediate
Trandolapril "Invest" clinical program	P	• Review trial in more detail (reduce complexity and risk)	• E. Fiorentino	• By May
Other trandolapril trials	C	• Continue "Create", "Peace" and "Benedict" trial programs	• Project team	• Ongoing
Fenofibrate	C	• Develop co-formulation ideas with Meridia and statins (including assessment of sales and costs)	• Project team	-
Depakote	C	• None identified	-	-
Gengraf	C	• None identified	-	-

**PLs' FZ**

**ABBOTT LABORATORIES**


**Clinical Study Report No. R&D/01/171**

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the  
Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful  
Diabetic Polyneuropathy**


**ABT-594/Protocol M99-114**

**31 July 2001**

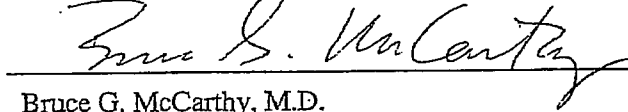
*I have read this report and confirm that to the best of my knowledge it accurately  
describes the conduct and results of the study.*

  
Marilyn J. Collicott  
Clinical Project Manager, Analgesia Venture

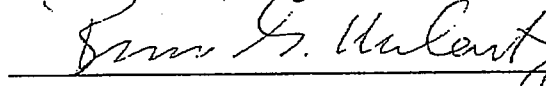
01 Aug 01  
Date

  
David D. Morris, Ph.D.  
Assistant Director, Statistics


03 Aug 01  
Date

  
Bruce G. McCarthy, M.D.  
Medical Director, Analgesia Venture

03 Aug 01  
Date

 FOR MARLEEN  
Marleen H. Verlinden, Pharm.D., Ph.D. VERLINDEN  
Vice President, Global Pharmaceutical Research and  
Development Neurology/Urology

03 AUG 01  
Date

 **Abbott Laboratories**

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ABT-594 (ABBOTT-165594)  
Study No. M99-114  
R&D/01/171 - Clinical/Statistical

i

## 1.0 Title Page

### ABBOTT LABORATORIES Clinical Study Report R&D/01/171

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy**

*ABT-594/Protocol M99-114*

Development Phase:	II
Investigators:	Multicenter
Date First Subject Dosed:	24 April 2000
Date Last Subject Completed Dosing:	24 February 2001
Sponsor/Signatory:	Marleen H. Verlinden, Pharm. D., Ph.D. Vice President, Global Pharmaceutical Research and Development Neurology/Urology D42U, AP30 200 Abbott Park Road Abbott Park, Illinois 60064-6145 Phone: (847) 935-4096 Fax: (847) 938-1629
Report Date:	31 July 2001

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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ABT-594 (ABBOTT-165594)  
Study No. M99-114  
R&D/01/171 - Clinical/Statistical

iii

**Methodology (continued):**

During the Primer and Treatment Phases, subjects were allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but were not allowed to take acetaminophen within 24 hours prior to a Treatment Visit).

Efficacy assessments included the Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change. Safety assessment included physical examination, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

No. of Subjects Planned and Enrolled:	Treatment Group	Planned	Completed/Enrolled
Planned: 320	Placebo	80	51/65
Enrolled: 266	ABT-594 150 µg BID	80	40/65
Completed: 138	ABT-594 225 µg BID	80	30/69
Premature Discontinuations: 128	ABT-594 300 µg BID	80	17/67
	TOTAL:	320	138/266

**Diagnosis and Main Criteria for Inclusion:**

Adult males and females at least 18 years of age, who weighed ≤265 pounds and who were judged to be in good health based on medical history, physical examination with vital signs, laboratory profile, and 12-lead ECG, who had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, good control (in the opinion of the investigator) of the their serum glucose for at least the last 3 months prior to the Screening Visit, and an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit, and who met all other selection criteria were eligible for study participation.

**Test Product, Dose and Mode of Administration, Batch Number:**

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Numbers
ABT-594 75 µg HGC, Formulation A-2	150, 225, and 300 BID	Oral	58-293-AR 61-312-AR

**Duration of Treatment:** 49 days

**Reference Therapy, Dose and Mode of Administration, Batch Number:**

Test Product	Dose (µg)	Mode of Administration	Drug Product Lot Number
Placebo for ABT-594 HGC	0	Oral	55-243-AR-01

**Criteria for Evaluations:****Efficacy:**

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation was analyzed in a similar manner. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to Day 1 of the study.

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ABT-594 (ABBOTT-165594)  
Study No. M99-114  
R&D/01/171 - Clinical/Statistical

46

## 9.8 Changes in the Conduct of the Study or Planned Analyses

### 9.8.1 Protocol Changes

Significant changes in the developmental strategy of ABT-594 resulted in the study being prematurely discontinued by the sponsor. Therefore, although the protocol specified that approximately 320 subjects (80 per treatment group) were to be enrolled, enrollment was stopped at 266 subjects.

The final clinical protocol incorporated Amendment Number 1. All subjects were enrolled under the final protocol (Table 14.1\_\_2). Full details of the clinical protocol and its amendment are presented in Appendix 16.1.1. Important changes included in the amendment are summarized below:

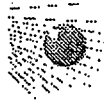
#### Amendment 1 (29 February 2000)

- Modified the inclusion criteria such that subjects were required to have good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit.
- Added that subjects with a hemoglobin A<sub>1c</sub> >11% were to be excluded.
- Added hemoglobin A<sub>1c</sub> at the Screening Visit and Treatment Visit IV and deleted the hemoglobin A<sub>1c</sub> at the Baseline Visit.
- Added mixed serotonin and norepinephrine reuptake inhibitors and St. John's Wort to the list of excluded medications.
- Added that the Screening hemoglobin A<sub>1c</sub> result served as the baseline result.

### 9.8.2 Statistical Changes

Although not specified in the protocol, efficacy analyses were also performed on a dataset that included subjects who did not prematurely discontinue from the study (study completers).

**PLs' GI**



Tamara L  
Garavalia /LAKE/PPRD/ABB  
OTT  
10/09/2001 10:25 AM

To Linda M Fisher/LAKE/PPRD/ABBOTT@ABBOTT  
cc  
bcc  
Subject ABT-594 Not Funded

So - now that you have a lot of free time - you can go out for lunch more often! (Ha Ha - bet you thought I was going to push another project your way!)

tg

--- Forwarded by Tamara L Garavalia/LAKE/PPRD/ABBOTT on 10/09/01 10:25 AM ---



Gary D Jones  
10/09/01 10:04 AM

To: D492  
cc: Patrick M Klemens/LAKE/PPRD/ABBOTT@ABBOTT  
Subject: ABT-594 Not Funded

FYI

--- Forwarded by Gary D Jones/LAKE/PPRD/ABBOTT on 10/09/01 10:03 AM ---

Howard S Cheskin  
10/09/01 09:44 AM

To: Claudia M Davila/LAKE/PPRD/ABBOTT@ABBOTT, David G Stroz/LAKE/PPRD/ABBOTT, Diana L Green/LAKE/PPRD/ABBOTT@ABBOTT, Erskine R Hilyer/LAKE/PPRD/ABBOTT@ABBOTT, Eugenia Gotsis/LAKE/PPRD/ABBOTT@ABBOTT, Jenny M Chan/LAKE/PPRD/ABBOTT@ABBOTT, Ji Zhou/LAKE/PPRD/ABBOTT@ABBOTT, Jim J Ciullo/LAKE/CAPD/ABBOTT@ABBOTT, John E Hengeveld/LAKE/CAPD/ABBOTT@ABBOTT, Linda M Fisher/LAKE/PPRD/ABBOTT@ABBOTT, Lloyd S Dias/LAKE/PPRD/ABBOTT@ABBOTT, Megan R Hughes/LAKE/PPRD/ABBOTT@ABBOTT, Michael L Branton/LAKE/PPD/ABBOTT@ABBOTT, Rhonda J Peck/LAKE/PPRD/ABBOTT@ABBOTT, Sanjeev Sharma/LAKE/PPRD/ABBOTT@ABBOTT, Shyamala C Jayaraman/LAKE/PPRD/ABBOTT@ABBOTT, Smriti S Desai/LAKE/PPRD/ABBOTT@ABBOTT, Stephen J Vigmond/LAKE/PPRD/ABBOTT@ABBOTT, Thomas J Myers/LAKE/PPRD/ABBOTT@ABBOTT, Victoria H Estrada/LAKE/PPRD/ABBOTT@ABBOTT, William T Monte/LAKE/CAPD/ABBOTT@ABBOTT  
cc: Ashok Katdare, Elraim Shek/LAKE/PPRD/ABBOTT@ABBOTT, Dana K Morgan/LAKE/PPRD/ABBOTT@ABBOTT, Richard A Pyter/LAKE/PPRD/ABBOTT@ABBOTT, Liam Feely, Gary D Jones/LAKE/PPRD/ABBOTT@ABBOTT, Steve Szostak/LAKE/PPRD/ABBOTT@ABBOTT  
Subject: ABT-594 Not Funded

An outcome of yesterday's Pharmaceutical Executive Committee meeting was to kill ABT-594. There will be attempts to outlicense the compound since the risk/value assessment came up with a positive net present value, but it will not be developed by Abbott.

Please discontinue all project activities related to the clinical supply. We will work out the close-down activities in the next couple of weeks.

Howard

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ABBOT148334

*Leiden* EXHIBIT *33*  
FOR I.D. *4-26-07* *1 gac*



**PLs' GJ**



From: Steven Kuemmerle, Ph.D.  
Director, Decision Support Group  
Dept: 4NP Ext: 7-3037  
Bldg: AP9A-2 Fax: 8-5290

**INTEROFFICE CORRESPONDENCE**

Date: 10/23/01

To: Keith Hendricks

cc: Liz Kowaluk John Simons Kevin Lynch  
Damien Springuel Jenny Dart Karen Erken

**RE: DSG HIGHLIGHTS: OCTOBER, 2001**

Portfolio Analysis (Complete): All. Analysis and package completed for October 8<sup>th</sup> review. This represented an outstanding effort by all PAG and DSG members.

Portfolio Analysis Improvements (Ongoing): All. Team is currently working on process, software and methods improvements. A PA improvements workshop, involving key members from SDG Inc., PAG and DSG was held on 10/17. Expect completion of the improvements effort in early 2002.

Oncology Phase-2 strategy (Modeling Alternatives): John & Kevin. Completion targeted for the second week in December. Team used initial characterization of oncology opportunities for 10/8 plan review. Currently assessing the need to proceed further with the analysis.

TAP PREVACID pricing strategy (Complete): Steve. Results of the analysis were used as basis for 2001 Prevacid LRP. There is a preliminary plan to re-assess in the December time frame.

ABT-594 / Pain (Complete): Liz. Development of ABT-594 has been discontinued. The analysis revealed that it was unlikely that -594 would be better than 2<sup>nd</sup> line, thus significantly limiting the opportunity.

CV Task Force (Part-2; assessment, modeling & alternatives): Steve. Preliminary recommendations (Part-1) were presented to senior GP and HPD management on September 26th. Currently working on building strategies and assessing opportunities for each (Part-2).

Schizophrenia (DTA201 & 190555) (Analysis suspended): Liz & Kevin. Novartis appears to have stopped work on DTA201. Recent SAC evaluation of 190555 was less than enthusiastic.

Adherivir (Frame): Steve & Kevin. Evaluation of strategies for various compliance added-value product concepts, focusing on Kaletra. Expect to begin October 30th.

ABT-963 (Frame): Liz & Karen. We have been asked to conduct an analysis of potential development strategies in the pain and oncology area. Initial discussions with key stakeholders begin this month.

ABT-492 (Frame): John & TBD. The compound has entered into Phase-2, thus we have been asked to conduct an analysis of potential development strategies for RTI,

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UTI, S&ST and other indications, in both the community and hospital arena. Initial discussions with key stakeholders begin this month.

Metabolic / obesity (Frame / profile): John. Facilitate development of product profiles for 2 new obesity drugs in the Metabolic therapeutic area. One of the drugs has not passed DDC, so we are re-evaluating what needs to be done for the remaining drug.

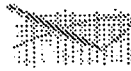
Synthroid (Frame & Alternatives): Liz & Karen. Evaluate a product life cycle strategy for Synthroid in light of potential product extension opportunities (e.g. T4/T3). An initial discussion with key stakeholders is ongoing.

Other. Please join me in a warm welcome to Karen Erken, who joined DSG as a Decision Analyst, October 1<sup>st</sup>. Actively recruiting for the 1 remaining open HC. The 3-day DDP workshop, scheduled for 9/12-9/14 has been postponed to 10/31-11/2. We are in discussions with outside consultants concerning support for a therapeutic area strategy project in 2002 (likely in the Psych area).

**PLs' GL**



**PLs' HK**



Christopher J Silber  
09/03/1999 09:33 AM

To: Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT  
cc: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT  
Subject: Re: Advice

Rose:

The bottom line is that both studies provide evidence that suggests that adequately powered trials could be performed that would show statistically significant differences in outcome measures. All things considered, using the broadest definition of success, neuropathic pain would seem to have an advantage as the first choice development target.

For OA, such a study *could* be conducted, I believe, at doses of ABT-594 used in our present pilot phase 2 study (ie, 50 and 75 mcg BID) without titration. While the overall benefit/risk profile of this regimen would be unfavorable (relative to NSAIDs), on the benefit side the magnitude of efficacy would be clinically meaningful, and would be reflected in outcome measures acceptable to regulatory authorities. So, for OA, depending on how narrowly you want to define success, it may already have been achieved. If titration mitigates the AE profile, the benefit/risk would become favorable if ABT-594 efficacy approximates that of NSAIDs, and further enhanced if efficacy is of *greater* magnitude than NSAIDs. Therefore, from a scientific/regulatory perspective, OA has a good likelihood of success. From a clinical perspective, I agree that titration represents some level of barrier to use in OA, unless some upside (beyond innovative mechanism) is identified (eg, no ulcers, greater efficacy), or segment of the market is amenable to titration (eg, severe pain, refractory to NSAIDs or current/history of ulcer disease).

For neuropathic pain, there are scant few regulatory precedents (as is usually the case in areas of unmet medical need), which adds some complexity: what are clinically meaningful improvements, what magnitude of change in which outcome measure(s) will be considered to form a sufficient body of evidence to support approval. Trends toward improvement are noted in the present study in a scale designed specifically for neuropathic pain, particularly in patients with diabetic polyneuropathy. In my opinion, doses used in our present pilot phase 2 study are unlikely to be sufficient (even in a larger, longer study of exclusively diabetic polyneuropathy) to support approval. So, for neuropathic pain, the goal of titration is to be able to get to higher doses (higher than 75 mcg BID) that I think are necessary to achieve a larger magnitude of efficacy than that observed in our present study. Relative to OA, a favorable benefit/risk profile in neuropathic pain could exist with a greater burden of AE's. Stated simply, available therapeutics for neuropathic pain don't work too well and/or have lots of side effects. Although from a scientific/regulatory perspective neuropathic pain has a more modest likelihood of success, when clinical utility is considered (patient acceptance of AEs, titration, paucity of available alternatives), neuropathic pain as a target seems to avoid the barriers posed by OA. All things considered, neuropathic pain would seem to have an advantage as a development target.

Chris

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**PLs' HS**

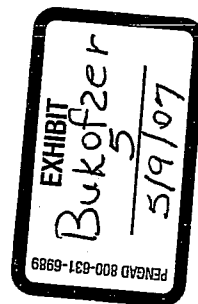


**May 1999**  
**ABT-773 Project Status Report**

**Key Issues/Decisions/Events**

Key Issues/Decisions/Events		Progress
CAPD	Availability and cost of bulk drug: 3 month delay in funding decisions has moved the filing date from Oct 2001 to Dec 2001. The COGS for a 2001 filing will be \$4000/kg at launch (optimistic).	An additional \$3MM of a required \$15MM was approved on Feb 3. Based on scaled-back assumptions, this allows purchase of rate-limiting bulk chemicals, but does not allow for process improvements necessary to reduce COGS. Incremental funding request in April Update of \$5.3MM and \$6.5MM in Blue Plan. Re-evaluation of bulk drug requirements completed in April. April Update funding for bulk drug to Aug Go/No Go decision approved at \$18.4MM.
CAPD/PARD	A change in bulk drug physical or chemical properties during formulation development will result in a delay in the Dec 2001 filing date. If at the 300L scale up to 12 months delay, if at the 1200L scale, up to 18 months.	Lock the final chemistry at the latest possible date. Current plan is Dec 99 to Jan 2000. Our best chance of success will be an IR formulation rather than an ER. Plan to maximize the number of bulk drug lots.
PARD	A once-a-day formulation may not be possible based on the short half-life of the drug and the apparent short absorption window in the GI tract (6-8 hrs.). The market share impact of QD is high.	Pursuing internal and external development of IR and ER prototypes (16) to evaluate in PK studies. First set of internal prototypes will be available May 10. First external prototypes estimated to be available June 30. Agreements with Elian and ALZA completed by March 31.
PARD	If one of our initial 5 (2 IR, 3 ER) out of 16 prototypes is not chosen as the final formulation, the Dec 2001 filing date will be delayed 4 to 6 months.	The 2 IR prototype PK evaluation studies to start May 18 <sup>th</sup> . ER prototype studies to start June 4 <sup>th</sup> . Decision on first 5 prototypes by August 1999.
NPD	QD dosing for adult tab/cap is necessary for commercial success. Market share impact of QD is high.	Initial internal IR prototypes will be available May 10 <sup>th</sup> . Initial ER prototypes will be available May 31 <sup>st</sup> .
Financial	Additional \$17.5MM funding required to meet a tablet filing date of Dec 2001. This does not include management judgement of approx. \$3MM.	April Update funding submitted Feb 15 for \$40.5MM vs Updated Plan of \$29.5MM (adult oral). Blue Plans submitted for \$6.5MM (adult oral), \$2.2MM (IV) and \$1.5MM (Peds). April Update funding approved at \$37.2MM to Aug Go/No Go decision. Remaining requirement of \$9.7MM to requested at that time.
Drug Safety	QD dosing may not be feasible due to less than 50% relative bioavailability with ER compared to IR. Market share impact of QD dosing is high.	Complete Intellisite study April 9 <sup>th</sup> to determine extent of release in the colon of ABT-773. Preliminary results available May 7 <sup>th</sup> . Assess role of P-glycoprotein in CACO2 cells, complete study May 1999.

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# May 1999 ABT-773 Project Status Report

## Business Rationale

Date: April, 1999  
Franchise: Anti-infective  
Venture: Macrolide

ABT #: ABT-773  
Trade & Generic Name: TBD, TBD  
Mechanism of Action: Ketolide, antimicrobial

## Development Timeline

	PPCCDDC 3/1997 (\$MM)	Plan as of 12/1998 (\$MM)
Cost to NDA (OT, Pre-IV)	260	N/A
Cost to Next Go/No Go (Phase IB, prototype eval)	—	284
Cum. Cost through 1998	—	37.2
1999 APJ Funding Request	—	29
1999 Plan (Funded)	—	47
• Current Projection	—	37.2
• YTD/LM	—	47
		62

## Development Timeline

Attribute	Date Defined	Probability*	Status	Share Impact
Activity against Gram +, atypical	3/1997	High	Confirmed	High
Activity against H. influenzae a and b	3/1997	High	Confirmed	High
Active against 80% of Gram - resistant strains of enteric and MLSC	3/1997	High	Confirmed	High
Active against most macrolide resistant pathogens on a bacterial-worldwide susceptibility panel	3/1997	High	Confirmed	High
Low incidence of GI side effects and oral	3/1997	High	Confirmed	High
Low incidence of drug-interactions = oral, no contraindications	3/1997	High	Confirmed	High
OD dosing schedule	3/1997	High	Confirmed	High
OD dosing per os	3/1997	High	Confirmed	High
BID dosing for IV	3/1997	High	Confirmed	High
Less metabolic waste for ER than oral	3/1997	High	Confirmed	High
500mg BID	3/1997	High	Confirmed	High
7-day therapy for most indications	3/1997	High	Confirmed	High
Oral solid dose at 300mg/day	3/1997	High	Confirmed	High
COGS (2003 Launch)	3/1997	High	Confirmed	High

\* Probability Key:  
High = 70-100%  
Medium = 30-60%  
Low = 0-20%

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	PPCCDDC 3/1997	Revised 6/1997	Current Review 1/1999
Patent Status:	9/2016	9/2016	9/2016
NDA Filing:	12/2000 (lab/cap)	12/2000 (lab/cap)	8/2002 (el)
ex-U.S. Filings:	9/2001 (OS, IV)	12/2000 (lab/cap)	8/2002 (el)
Projected U.S. Launch:	9/2001 (OS, IV)	4/2002 (lab/cap)	9/2003
Projected ex-U.S. Launches:	12/2003 (OS, IV)	4/2002 (lab/cap)	9/2003
Peak TRK Share*, U.S.:	4.4% TC: 4.7% OS: 3.3% IV	4.4% TC: 4.7% OS: 3.3% IV	4.4% TC: 4.7% OS: 10% IV
Peak TRK Share, ex-U.S.:	N/A	N/A	3.3% TC: N/A OS, 10% IV
Peak Sales, U.S. (\$MM)	\$420 TC: \$118 OS	\$380 TC: \$75 OS	\$380 TC: \$580 OS
Peak Sales, ex-U.S. (\$MM)	\$26 IV	\$22 IV	\$13.8 IV
Pre-Tax NPV @ 15% U.S. (\$MM)	N/A	N/A	\$360 TC: N/A OS, \$200 TC: \$5.1C (\$1.1V)
Pre-Tax NPV @ 15% ex-U.S. (\$MM)	N/A	\$28 TC: (\$7) OS	\$240 TC: N/A OS, before cannibalized or oral
Target Drug Costing at Launch	\$116 TC: \$277 OS	\$116 TC: \$277 OS	\$121 TC: N/A OS, IV after cannibalized or oral
SMM at Launch	\$3720 IV	\$3720 IV	\$363 TC: \$291C \$893 IV
SMM at Year 5	—	77% TC: 60% OS: 95% IV	85% TC: 83% OS: 1V
		77% TC: 60% OS: 95% IV	104% TC: 82% OS: 1V

**May 1999**  
**ABT-773 Project Status Report**

**Project Overview**

Description	PPC/DDC Date	No Other Plan	Plan 1998
PPCC Approval	3/1997		3/1997
Start Phase I (adult oral)	11/1997		12/1997
Go/No Go Clinical Safety	6/1998		10/1998
Start Phase II (adult oral)	7/1998		12/1998
Go/No Go Clinical Efficacy	12/1998		7/1999
Phase I (Peds, IV)	6/1999		TBD
Start Phase III (adult oral)	1/1999		9/2000
File NDANMEIA (adult oral)	12/2000		12/2001
Phase III (Peds, IV)	TBD		TBD
File NDANMEIA (Peds, IV)	TBD		TBD
Regulatory approval (adult oral)	12/2001		12/2002
Regulatory approval (Peds, IV)	TBD		TBD

Drug Substance Source/Lot #	KG Orig/Revised	Plan 12/1998	Actual Date	Actual/Projected Cost/kg*
35-529-NI-00	NA/25.3	1/1998	1/1998	\$30,000
37-459-YS-00	NA/25.4	3/1998	3/1998	\$30,000
40-573-NI-00	NA/20.5	5/1998	5/1998	\$30,000
40-575-NI-00	NA/8.1	5/1998	5/1998	\$30,000
45-624-NI-00	NA/23.1	10/1998	10/1998	\$30,000
50-007-CA	200/209	2/1998	2/1998	\$10,000
Campaign 2	NA/200	6/1999		\$10,000
Campaign 3	NA/300	9/1999		\$10,000
Campaign 4.5	NA/700	12/1999		\$10,000
Campaign 6.7.8	NA/800	3/2000		\$8,000
Campaign 9.10.11	NA/900	6/2000		\$8,000
Campaign 12.13.14	NA/900	9/2000		\$8,000
Campaign 15.16.17	NA/900	12/2000		\$8,000
Campaign 18.19.20	NA/900	4/2001		\$5,000

\*Represent cost of drug substance at launch (Data 2001) is \$4,000/kg (P-NI oral)

Activity	Plan N/A	Plan 12/1998	Actual 12/1999
Phase I Formulation (Caps)	—	12/1997	12/1999
Phase II Formulation (Tablet)	—	7/1999	
Clinical Supplies Phase IIB	—	7/1999	
Phase III Formulation (Tablet)	—	4/2000	
Phase III Clinical Supplies Manufactured	—	9/2000	
NDA Lots (3) Completed	—	7/2000	
Completion of 1 Year Stability for NDA	—	8/2001	

Toxicology Activity	No Other Plan	Plan Start 12/1998	Actual Start Date	Rep Compl
2-week oral Rat/Monkey	—	7/1997	6/1997	8/19
Acute Studies	—	8/1997	8/1997	12/11
Mouse Lymphoma/Micronucleus	—	11/1997	11/1997	4/19
1 Month Rat/Monkey	—	12/1997	12/1997	12/11
Pregnant Rat/Rabbit RF	—	1/1998	1/1998	11/11
SEG II Rat/Rabbit	—	3/1998	3/1998	2/19
Guinea pig sensitization	—	11/1998	11/1998	2/19
3 Month oral Rat/Monkey	—	10/1999		
Seg III Rat	—	10/1999		
IV Irritation studies	—	6/1999		
Neonatal/Juvenile Rat	—	10/1999		

ABT 0004846  
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# May 1999 ABT-773 Project Status Report

## Clinical Study Progress

Protocol: ABT-773 (Efficacy and Safety Study)  
Objective: Determine extent of release in the colon of ABT-773.

Evaluate Safety and efficacy of a 7 day course of therapy with an or IR formulation, and to determine the PK of 773 within a subset of those subjects.

100 mg TID or 200 mg TID

None

150

\$1,500M

200 mg single dose

773 capsule and solution

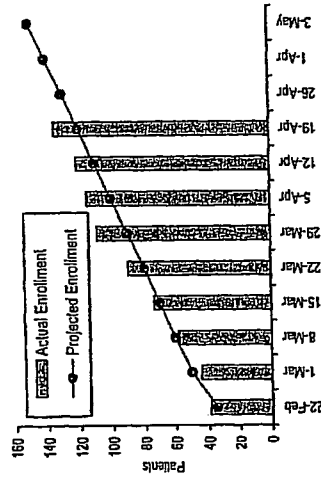
8

\$120,000

Started 03/05/99, to completed 4/10/99.  
Preliminary results to be available May 7.

Ongoing, 135 subjects enrolled in Europe. To complete by April 30, study report by June, 1999.

Of 45 cases assessed, 100% showed clinical cure. 70 pathogens have been identified, 16 *S. pneumoniae*, 30 *H. flu.*, 9 *M. cat.*, 15 *H. parainfluenzae*.



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**May 1999**  
**ABT-773 Project Status Report**

**Clinical Study Progress**

<b>Protocol</b>	ABT-773 PK BID	ABT-773 PK TID
<b>Objective</b>	To determine the PK profile of BID dosing, to determine feasibility of proceeding with a planned efficacy trial and to link PK to efficacy.	PK link to efficacy of M98-967. First IND study.
<b>ABT-773 Doses</b>	100 mg BID vs 200 mg BID	100mg TID vs 200mg TID
<b>Comparator Doses</b>	None	None
<b>Target Enrollment</b>	24	12
<b>Target Cost</b>	\$150,000	\$100,000
<b>Actual Cost</b>	TBD	TBD
<b>Status</b>	Started 3/2/99, to completed 3/21/99.	Started 3/8/99, to completed 3/27/99.
<b>Major Findings</b>	Review of preliminary results in-process.	Review of preliminary results in-process.

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**May 1999**  
**ABT-773 Project Status Report**

**Clinical Study Progress**

Project	ABT-773
Objective	To determine concentration compared to plasma levels. Evaluate probability of success with QD, especially with H. Flu. Link with efficacy and plasma levels.
ABT-773 Doses	100 mg X 2 QD
Comparator Doses	None
Major Endpoints	40-45
Major Cost	\$190,000
Actual Cost	TBD
Status	Started 4/19/99, to complete 6/30/99.
Major Findings	—

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**May 1999**  
**ABT-773 Project Status Report**  
**TABLET ONLY, DEC 2001 FILING**

	1997 Actual	1998 Actual	Cumulative Thru 1998	1999 Plan	1999 APU	Cumulative Thru 1999	2000 Plan	Cumulative Thru 2000	2001 Plan	Cumulative Thru NDA
Clinical Program	0.5	5.2	5.7	9.8	12.1	17.8	24	41.8	46	87.8
INDUSTRY/PHARMACEUTICAL	7.4	15.5	22.9	11	30.8	53.7	28	81.7	27	108.7
INDUSTRY/PHARMACEUTICAL	1.0	3.4	4.4	2.8	3.4	7.8	6	13.8	6	19.8
INDUSTRY/PHARMACEUTICAL	1.4	4.9	6.3	2.9	0.7*	7	8	15	8	23
INDUSTRY/PHARMACEUTICAL	10.3	29	39.3	26.5	47	86.3	66	152.3	87	239.3
INDUSTRY/PHARMACEUTICAL				29.5 (approved \$3MM post-Plan)						

\*Includes a management judgement of approx. \$3MM. 1999 April Update currently funded at \$37.2MM to Aug Go/No Go decision. Remaining \$9.8MM to be requested via Blue Plan based on a favorable decision.

File NDA = 12/2001

Clinical Program = grants, data mgmt/stats, venture management

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**PLs' HW**



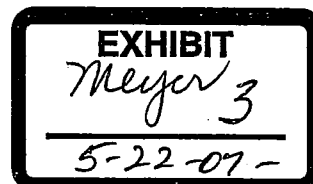
**ABT-773**  
**KETOLIDE ANTIBIOTIC**

**2000 Strategic Marketing Plan**  
**June 2000**

**Rod Mittag**  
**Manager, New Product Development**

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*ABT-773 Strategic Marketing Plan*



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*The objective of this strategic document is to develop a common foundation for the commercial development of ABT-773. This plan includes the strategy for execution of the strategic marketing plan.*

*This document presents the domestic marketing plan for ABT-773. An ex-U.S. marketing plan will be developed by Abbott International New Product Planning.*

TABLE OF CONTENTS

	<u>PAGE</u>
I. EXECUTIVE SUMMARY	1
II. INTRODUCTION	2
III. MARKET OVERVIEW	3-8
IV. UNMET NEEDS	9
V. PRODUCT PROFILE	10
VI. PRODUCT OBJECTIVE, POSITION, MESSAGE	11
VII. KEY COMMERCIAL ISSUES/OPPORTUNITIES AND STRATEGIES	12-17
VIII. STRATEGIC MARKETING MIX	18-19

## I. EXECUTIVE SUMMARY (NOT REVISED)

ABT-773 is a ketolide antibiotic currently under development by PPD. A tableted formulation is currently being evaluated in Phase II clinical studies. Indications are being sought for acute bacterial exacerbations of chronic bronchitis (ABECB), community-acquired pneumonia (CAP), and acute maxillary sinusitis (AMS).

It is anticipated that ABT-773 will file with the FDA in December 2001 and be approved December 2002.

I.V. and oral suspension (pediatric) formulation development has not yet been funded, though funding is anticipated for FY2000. Development plans for these formulations are being established.

Total U.S. antibiotic sales in 1998 were \$7.7 billion, comprised of \$4.8 billion in tab/cap sales, \$1.9 billion in pediatric sales, and \$1.0 billion in I.V. sales. While the use of antibiotics has been decreasing (TRX CAGR<sub>95-98</sub> of -3.5%), sales of antibiotics has been increasing (Sales CAGR<sub>95-98</sub> of +3.4%). Key market drivers are:

- Resistance to antibiotics will continue to increase. Physicians will be urged to restrict the use of antibiotics for documented, severe infections and to choose agents with an appropriate spectrum of activity relative to the infection being treated.
- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant competitive threat. Up to five new quinolones will reach the market prior to ABT-773.
- Convenience attributes such as QD dosing and short course of therapy (5-7 days) will become commonplace and will offer little in the way of differentiation; adverse events and drug-drug interactions will continue to be important attributes.
- Unmet need in the antibiotic market is very low. Companies will turn to new efficacy metrics as a means of differentiating their products. Efficacy toward resistant organisms will be an important new metric. PK/PD parameters will also be exploited to gain competitive advantage.
- Several key branded antibiotics will lose patent exclusivity over the next three to five years, resulting in increasing price sensitivity within the antibiotic market. This will create opportunity in the pediatric market, however, as the top three pediatric brands are among those losing patent exclusivity.
- Two antiviral influenza agents will reach the market in 1999, with others likely in the future. Given that a considerable amount of antibiotic business stems from inappropriate use for influenza, the companies launching these agents will likely exploit the increasing of awareness of appropriate use and encourage physicians forgo the use of antibiotics in lieu of the new antiviral agents. Increasing use of currently available point-of-care diagnostic kits will allow physicians to distinguish bacterial infection from influenza.

The success of ABT-773 will depend on the extent to which it can differentiate itself from this competitive field.

## II. INTRODUCTION

Ketolides are a relatively new class of antibiotics that are based on a macrolide-like structure. The ketolide ABT-773 is being evaluated in the treatment of acute exacerbations of chronic bronchitis (AECB), tonsillitis/pharyngitis, community-acquired pneumonia (CAP), and acute bacterial sinusitis.

A Phase IIa bronchitis study was completed in June 1999. Based on this study and on phase I PK and formulation studies, a "Go" decision was made to continue development. Phase IIb dose-ranging studies were initiated in September 1999 with 150 mg, 300 mg, and 600 mg QD formulation for in AECB (5 days), CAP (7 days), and sinusitis (10 days; 150 mg was not evaluated in sinusitis). Results of these phase IIb studies are summarized in Table 1.

Table 1: Summary of Phase IIb Clinical Results

	AECB			CAP		Sinusitis		
	150 mg	300 mg	600 mg	300 mg	600 mg	150 mg	300 mg	600 mg
<b>Clinical Cure</b>	87%	90%	90%	92%	80%	89%	83%	71%
<b>Eradication</b>								
-S. pneumo	84%	90%	100%	87%	100%	3/3	8/8	9/12
-H. flu	94%	89%	83%	100%	72%	3/5	7/7	5/7
-M. cat	80%	92%	91%	6/8	2/4	8/9	3/4	4/4
-Overall	86%	89%	92%	92%	79%	77%	96%	78%
<b>AEs</b>								
-Diarrhea	13%	12%	21%	12%	17%	6%	6%	17%
-Taste	6%	19%	29%	17%	26%	1%	14%	27%
-Nausea	7%	13%	30%	12%	21%	3%	12%	26%
-Vomiting	2%	3%	11%	8%	13%	1%	6%	17%

The primary conclusions of these studies were: a) adverse events at 300 mg and above were too high to support a commercially viable product b) there was no statistical difference between doses from an efficacy (cure or eradication) standpoint.

The decision was made to proceed forward into phase III with a 150 mg QD dosing strategy for all indications. The decision to pursue this strategy alone would have resulted in considerable risk stemming from a) a moderate risk of clinical failure in the relatively difficult-to-treat indications of CAP/sinusitis b) the risk that the entire package could be dismissed by ex-US regulatory agencies should either the CAP or sinusitis clinical data be substandard. Therefore, a backup strategy was added to the core program to mitigate this risk. The clinical program to NDA is summarized below.

Figure X: Summary of Clinical Strategy to NDA

Development of IV and OS formulations was initiated in late 1999. Phase I studies on the IV formulation will be initiated X 2000; phase I studies on the OS formulation will be initiated June 2000.

The NDA filing for ABT-773 tablets is expected in December 2001 with an anticipated US market launch of December 2002. The IV and OS NDA filings are expected in December 2002 with an anticipated US market launch of December 2003.

### III. MARKET OVERVIEW

#### A. Epidemiology

Table 1: U.S. Prevalence of Bacterial Diseases by Diagnosis-MM

Otitis media	Sinusitis	Pharyngitis	Pneumonia	AECB
18.2	40.4	10.6	2.5	17.7

#### B. Market Data

Table 2: 1995-1999 U.S. Antibiotic Market

U.S.	TRXs (MM)		1995	1996	1997	1998	1999	CAGR <sub>95-99</sub>
		Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

The U.S. tab/cap, oral suspension, and I.V. markets had 1999 sales of \$5.7B, \$1.1B, and \$2.1B respectively. Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics (approximately 30MM fewer generic antibiotic prescriptions were written in 1999 than in 1995). So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Table 3: 1999 U.S. Tab/Cap Antibiotic Market-Sales and TRX

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$881.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
<b>TOTAL TAB/CAP</b>	<b>\$5,715.4</b>	<b>100.0%</b>	<b>8.9%</b>	<b>221.5</b>	<b>100.0%</b>	<b>0.1%</b>

Table 3 shows 1999 tab/cap sales and prescriptions by class/product. Macrolides, fueled largely by gains in Zithromax, and quinolones, fueled largely by gains in Levaquin, have done very well in terms of both prescriptions and sales. The growth of these classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin. Zithromax prescriptions sales are closing in on the sales leader Cipro and far outnumber those of other competitors. Increasingly, the RTI market is coming to be dominated by two antibiotic classes, macrolides and quinolones. Quinolones have been able to leverage their activity against resistant Strep. pneumoniae and H. influenzae to become direct competitors to macrolides in the RTI market; a number of new entrants (moxifloxacin, gatifloxacin, gemifloxacin) will add to the competitive pressure. In essence, the market is being asked to make trade-offs between the real or perceived weaknesses of the macrolides (H. influenzae, resistant Strep. pneumoniae, GI events [clari]) against those of the quinolones (safety, too broad spectrum, potential for resistance development).

Table 4: 1999 U.S. Oral Suspension Antibiotic Market

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$61.5	5.5%	-10.5%	26.7	43.9%	-7.1%
Ceph	\$375.7	33.5%	-10.8%	11.5	18.9%	-11.4%
Cefzil	\$168.3	15.0%	8.0%	3.9	6.4%	4.1%
Other Ceph	\$207.4	18.5%	-18.4%	7.6	12.5%	-16.0%
Ext. Spec. Macrolides	\$250.4	22.4%	30.9%	8.5	14.0%	39.1%
Biaxin	\$66.0	5.9%	-3.1%	1.6	2.6%	-7.0%
Zithromax	\$184.5	16.5%	108.6%	6.9	11.4%	165.3%
Augmentin	\$382.3	34.1%	17.2%	7.9	13.0%	10.2%
Other Classes	\$50.0	4.5%	-15.9%	6.2	10.1%	-18.3%
<b>TOTAL PEDIATRIC</b>	<b>\$1,119.8</b>	<b>100.0%</b>	<b>1.0%</b>	<b>60.8</b>	<b>100.0%</b>	<b>-5.4%</b>

Table 4 shows 1999 U.S. pediatric antibiotic sales and prescriptions by class/product. Augmentin, Zithromax and Cefzil are the market leaders, all of which have grown over the 1995-1999 period.



**Table 5: 1999 U.S. I.V. Antibiotic Market**

The following table shows 1999 U.S. I.V. antibiotic sales. Sales of I.V. antibiotic products have grown slightly as more expensive branded agents (Rocephin, Levaquin) have replaced lower cost generic agents. Rocephin, the market leader, had 1999 sales of \$514MM.

	Sales		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$69.1	3.3%	-3.6%
Carbapenem/Primaxin	\$139.3	6.6%	4.4%
Vancomycin	\$73.7	3.5%	-1.1%
Cephalosporins	\$904.9	42.7%	-1.9%
Rocephin	\$514.3	24.3%	4.0%
Other Cephalosporins	\$390.6	18.5%	-7.6%
Ery & Macrolides	\$45.5	2.2%	8.8%
Ext. Spec. Macrolides	\$35.3	1.7%	NA
Zithromax	\$35.3	1.7%	NA
Monobactams	\$331.4	15.7%	1.2%
Aminoglycosides	\$63.3	3.0%	1.7%
Quinolones	\$340.5	16.1%	21.4%
Cipro	\$120.5	5.7%	NA
Trovan	\$35.6	1.7%	NA
Levaquin	\$178.7	8.4%	NA
Other Classes	\$113.7	5.4%	21.5%
<b>TOTAL I.V.</b>	<b>\$2,116.8</b>	<b>100.0%</b>	<b>3.2%</b>

### C. Key Market Drivers

- Resistance to antibiotics will continue to increase. Physicians will be urged to restrict the use of antibiotics for documented, severe infections and to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant pathogens (Levaquin's recent claim for penicillin resistant *S. pneumoniae*) and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, etc) may confer competitive advantage to such agents.
- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs. The performance of recent quinolones along two dimensions may have a profound impact on the success of this class in the community RTI market: a) safety and b) development of quinolone resistance
- Convenience attributes such as QD dosing and short course of therapy (5-7 days) will become commonplace and will offer little in the way of differentiation; adverse event profiles and drug-drug interactions, however, are areas where improvements may be made.
- Unmet need in the antibiotic market is very low. Differentiation along current product attributes (clinical success, safety, convenience) will be difficult. Hence, companies will turn to new efficacy metrics as a means of differentiating their products. Efficacy toward resistant organisms will be an important new metric. PK/PD parameters will also be exploited to gain competitive advantage.

- Several key branded antibiotics will lose patent exclusivity over the next three to five years (see Table 6). Among those products losing patent exclusivity are the top three pediatric brands (Augmentin, Cefzil, Zithromax). While the influx of generic competition may result in increasing price sensitivity, the extent of the price sensitivity may be dampened in comparison to other markets where products do not lose their activity over time like antibiotics.

**Table 6: Anticipated Loss of Patent Exclusivity**

Augmentin	2002
Ceflin	2003
Cipro	2003
Dynabac	2003
Blaxin	2005
Cefzil	2005
Levaquin	2005
Zithromax	2005

- Antiviral therapeutics and diagnostics for influenza and colds will reach the market. While initial data suggest such agents may instead be used in an additive mode to antibiotics, increasing promotional support of such agents or a market increase in antibiotic resistance could alter this algorithm.

#### **D. Customers**

The bulk of antibiotic prescriptions are written by primary care physicians (GP, FP, IM, DO and Peds) and as such these physicians are the primary target market. Several specialties are also important, particularly from the standpoint of opinion development; these include infectious disease specialists, otolaryngologists (ENTs), allergists, and pulmonologists. Managed care is also a key customer, and strategies are being implemented to ensure the highest degree of formulary acceptance.

#### **E. Competitive Analysis**

Three classes of antibiotics represent the majority of the competition within the antibiotic market, namely ketolides, macrolides, and quinolones.

Whereas quinolones were once regarded as agents to be used only in cases of severe and/or non-respiratory infections, improvements in the safety and spectrum of these agents has allowed for increasing penetration into the community-acquired respiratory market. Two new quinolones, Tequin (gatifloxacin, BMS) and Avelox (moxifloxacin, Bayer) were launched in the U.S. in December 1999; a third, Factive (gemifloxacin, SKB) was filed with the FDA in December 1999. Beyond being highly competitive products from a product profile standpoint, the companies are also aggressively promoting these agents, each factor adding considerably to the competitive intensity within the community-acquired respiratory market. Tequin has fared well since its launch, outpacing the launch of the quinolone Levaquin by approximately X%. Quinolones are among the most active anti-infective classes in terms of number of compounds in development. Notable quinolones in development are T-3811 (Toyama/BMS), XXX, and XXX.

Macrolides are regarded as extremely safe and efficacious agents, but resistance to these agents, particularly with *Strep. pneumoniae*, is becoming more widespread. At the present time, resistance to macrolides is observed primarily in the context of in-vitro-based surveillance studies and has not yet resulted in a large number of clinical failures. Over time, however, macrolide resistance will reach a point that the clinical utility of these agents will be compromised.

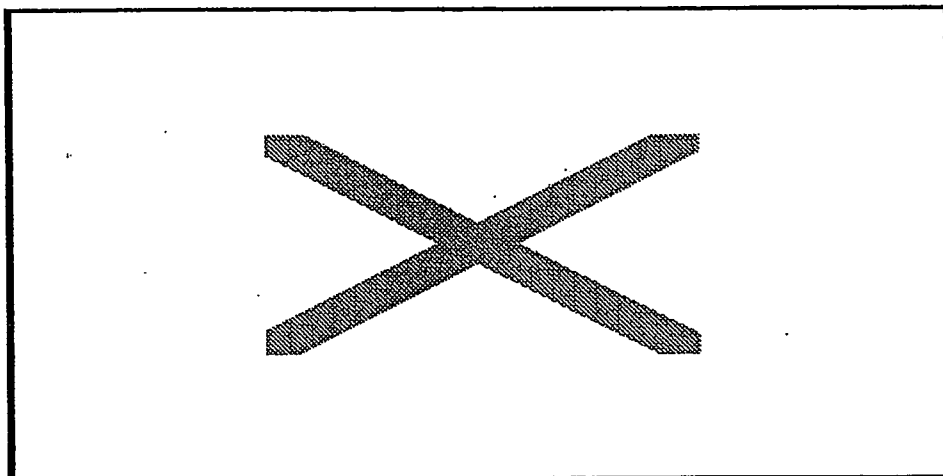
The response to this shortcoming of the macrolides are ketolides. Based on a macrolide structure, ketolides have improved microbiological activity against *Strep. pneumoniae* due to enhanced interactions with the ribosome. Ketek (telithromycin, Aventis) was filed with the FDA in March 2000, and will therefore likely be the first ketolide to reach the market. This first-to-market advantage may be relatively minor, however, as competitive intelligence has revealed limitations with the product including a relatively large dose (2 x 400 mg QD) and high COGS (which may limit its positioning flexibility). Scientific data presented at ICAAC 2000 also reported a high level of diarrhea (10-20%, see Appendix X for a full Ketek summary).

Zyvox (linezolid, Pharmacia), which represents the first agent of another novel class, oxazolidinones, was approved in the U.S. in April 2000. Zyvox has good coverage of Gram-positive pathogens such as *Strep. pneumoniae* and VRE but limited coverage of Gram-negative

and common community pathogens *H. influenzae* and *M. catarrhalis*. As such, placement of this product for community respiratory infections will be a challenge. Bayer and Zeneca are also pursuing oxazolidinones for anti-infective application in addition to Pharmacia.

A summary of the key emerging products is shown in Table 8.

**Table 8: Summary of Key Emerging Competitors**



#### IV. UNMET NEEDS

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, and this will likely continue and intensify over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation.

**Table 9: Unmet Needs in Anti-Infective Market**

Unmet Need	Pipeline Impact
Appropriate spectrum	As resistance continues to be an issue, the goal will be to match the spectrum of activity with the infections being treated. Macrolides have an appropriate RTI spectrum, but suffer from relatively poor activity against <i>H. influenzae</i> , a key respiratory pathogen. Quinolones cover the RTI spectrum, but are regarded by many to be too broad, also having activity against non-RTI Gram-negatives and anaerobic species.
Activity against resistant organisms	<i>S. pneumoniae</i> , MRSA, and VRE represent most problematic pathogens, though MRSA/VRE are not major community pathogens; efficacy against some G (-) pathogens (e.g. <i>Pseudomonas</i> ) is also becoming problematic. Most agents in pipeline offer increased efficacy against some resistant organisms but not others. Resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. It is unclear how quickly resistance will build to new classes of drugs. Gatifloxacin is touting that its 8-methoxy sidechain results in lower rates of resistance development; the role of PK profile in the development of resistance is also an emerging concept.
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing, may start to see 3-day therapies for some indications (AECB)
Increased tolerability	Key areas remain GI and taste perversion (macrolide/ketolide) and QT prolongation (macrolide/quinolone). As the market continues to mature, the market will be less tolerant of any significant level of AE.
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact to varying degrees with other drugs; a potent drug with no interactions would be a benefit in this market

#### V. PRODUCT PROFILE

The product profile shown below compares the optimal product attributes with those of ABT-773. The performance of ABT-773 for many of these attributes has not yet been determined. This profile is based largely on product attributes the current market values and promotes. As better and better agents reach the market, the marketing significance of many of these attributes will decrease and will no longer serve to differentiate products. Efforts are underway to identify

new and relevant product attributes that would confer competitive advantage to ABT-773 (see section VII).

**Table 10: Optimal Product Profile Versus Actual**

Optimal Product Attribute	Actual	Impact/Comments
Improved activity against G+ and atypical pathogens vs clarit	Same	Better activity than quinolones
H. flu activity comparable to moxifloxacin	Improved vs clarit/azi; inferior to moxi	Issue can be mitigated with clinical data and favorable tissue concentration data
Indication for drug resistant S. pneumo*	TBD	M

## VI. PRODUCT OBJECTIVE, POSITION, & MESSAGE

Two poles to market: safety/convenience vs efficacy

Market convergence

2<sup>nd</sup> tier differentiators i.e. ribosomes, pack strategy

Maximization of profit to the anti-infective franchise is the objective. This will be effected through an optimal positioning of all the agents in the franchise, including ABT-773, Biaxin, Biaxin XL, and any future product additions. This is not necessarily the positioning strategy that will result in the highest combined product share.

Product positioning is simply an identification of the differentiating characteristics of a product followed by the marketing (positioning) of the product to the market segment(s) that value those characteristics. The "box" strategy has been a useful construct in segmenting the current antibiotic market for Biaxin. This "box" strategy is based on marketing research that indicated that the severity of the illness usually was the most significant driver of antibiotic selection for physicians. For less severe "box 2" infections (which may actually be viral), convenience and cost are the main drivers of selection, with efficacy secondary. For more severe "box 3" infections, efficacy drives the decision, followed by convenience and cost. The marketing research also revealed that physicians perceived Biaxin to offer a high degree of efficacy. The "box" strategy was simply a realization of the differentiating characteristics of Biaxin (efficacy) and the promotion of that feature to the segment that valued it.

What must first be determined is whether the "box" (i.e. severity-based) segmentation will still be relevant to the market of 2003. If this "box" segmentation remains relevant, the differentiating characteristics of ABT-773 relative to this segmentation must then be assessed. Based on what is currently known of ABT-773, it will likely not be differentiated from other competitors based on convenience attributes. As such, it would be difficult to position the product as a pure "box 2" agent. The only other option would be to position the product along efficacy dimensions. The challenge here is that it is becoming increasingly difficult to differentiate products along current efficacy metrics such as clinical success, eradication, and spectrum of activity.

Over the next several months, New Product Development will be working with Venture and Marketing to define a "wish list" of potential differentiating clinical outcomes to allow positioning flexibility. These outcomes will then be evaluated in marketing research along with various positioning strategies (position, message, price). The scenario that affords the highest return to the franchise will form the basis for the positioning strategy for ABT-773. This research will also form the basis for the phase III clinical trial plan.



## VII. KEY COMMERCIAL ISSUES & OPPORTUNITIES

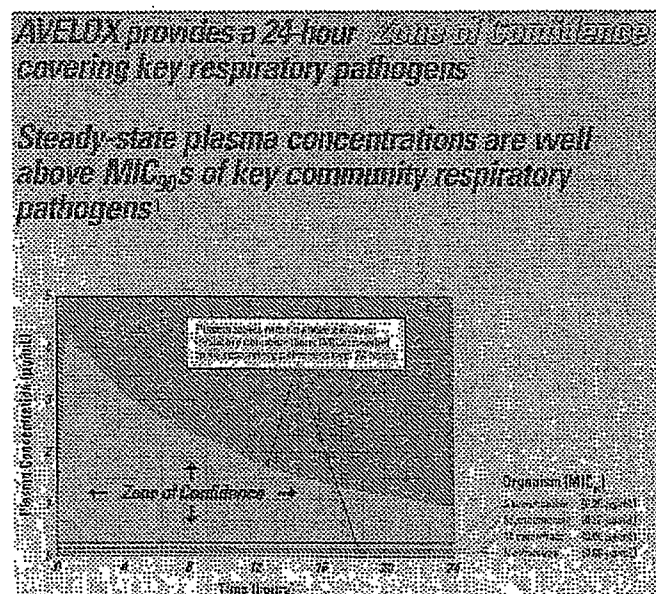
### A. ISSUES

#### Issue #1

Uncertainty in ABT-773 convenience profile i.e. potential for BID dosing

#### Issue #2

PK Profile (both serum and tissue)



#### Issue #2

Product Differentiation

#### Implication

At one time it was possible to differentiate antimicrobial agents through differences in key product attributes such as clinical efficacy, spectrum of coverage, dosing convenience and adverse events. Agents now reaching the market, however, are virtually identical with respect to these attributes, making product differentiation extremely difficult; this will be even truer when ABT-773 launches in 2003 (Table 11). Other sources of product differentiation beyond the traditional product attributes must therefore be identified and exploited.

#### Objective

Identify new metrics for product differentiation for ABT-773



### Strategies

Pharmacokinetic and pharmacodynamic (PK/PD) data is starting to emerge as a new source of product differentiation. It appears that moxifloxacin and gemifloxacin are both employing this strategy to differentiate themselves from other quinolones as well as from agents in other classes. The impact of these strategies should be taken very seriously given that 1) both Bayer and SKB are experienced players in the AIF market 2) they each employ a large number of sales representatives in the AIF market 3) the concepts put forth by the companies are virtually identical, in effect "colluding" to distance themselves from the crowded AIF market. A similar PK/PD strategy should be adopted for ABT-773 as well, at a minimum to neutralize any competitive advantage that could be realized by the competition (mainly the quinolones) but ideally to identify characteristics of ABT-773 which could be used to gain competitive advantage in its own right. Specifically:

- Concentration-dependent killing (quinolones) may be promoted as an advantage to time-dependent killing (macrolides/ketolides), implying an advantage in speed/efficacy as well as with induction of resistance ("dead bugs can't mutate"). If possible, work should be carried out to show comparable and/or superior kill kinetics to the quinolones. Such data would be used in conjunction with a marketing effort to distance the ketolide class from the negative PK/PD perceptions of the macrolides.
- The ratio of area-under-curve (AUC) to MIC is increasingly being adopted as a predictor for clinical outcome; at issue is the extent to which this ratio could be used as a promotional tool. While this ratio is applicable only to agents with concentration-dependent killing, the risk is that with enough promotional noise from the quinolones, prescribing physicians could erroneously start to apply this concept to agents like ABT-773 whose ratios might appear inferior (even if irrelevant) to those of the quinolones. Work should be carried out to determine if this ratio has any applicability to ABT-773 so that any efforts to promote agents over ABT-773 on the basis of this (misapplied) parameter can be blunted.
- Identify other PK/PD parameters where ABT-773 would have an advantage and where a compelling argument could be put forth as to the relevance of that parameter to the treatment of respiratory infection. Beyond that, considerable effort will need to be invested in the infectious disease community (opinion leaders, clinical study leaders, etc) to gain buy-in on these concepts. This will require the coordination of the Abbott scientists, venture members, marketing, and external collaborators to identify and implement such parameters.

Potential sources of differentiation beyond PK/PD should also be investigated. These might include:

- "Lifestyle" clinical outcomes, such as symptom improvement scores and onset of symptom improvement
- Pharmacoeconomic outcomes
- Post-antibiotic-effect
- Other respiratory pathogens e.g. *B. pertussis*
- New means of presenting adverse events i.e. not only by frequency but by the clinical significance of the adverse event

Over the next several months, New Product Development will be working with Venture and Marketing to define a "wish list" of potential differentiating clinical outcomes to allow positioning flexibility. These outcomes will then be incorporated into a positioning study (see issue #2) to determine the value of these outcomes to the market. Those outcomes deemed to have a sufficiently high ROI will then be recommended for inclusion into the phase III clinical trial plan.

**Issue #2**

Optimal product positioning

**Implication**

The positioning of ABT-773 must be carried out not only in regard to the overall antiinfective market, but also with respect to Biaxin, Biaxin XL, and Omnicef. The goal of the positioning strategy should be to maximize profit to the franchise, which may not be the strategy that maximizes combined franchise product shares.

Product positioning will also impact the extent to which the ketolide class can sell itself as a new class of antibiotics rather than merely an extension of the macrolide class. A new class would see less resistance in terms of formulary acceptance and would allow the class to distance itself from some of the negative perceptions of the macrolide class (H. flu, bacteriostatic, macrolide resistance).

As described above, the clinical trial plan should ultimately support the product positioning.

**Strategies:**

Primary marketing research will be carried out to determine the strategy that maximizes profit to the franchise. The objective of this research would be to identify the positioning (position, message, price) that offers the highest profit return to the franchise in light of the competitive landscape. This work will be in progress from November 1999 through January 2000. The product positioning will drive the phase III clinical trial plan. It is anticipated that the phase III clinical plan will need to be completed by February 2000.

**Issue #3**

The HMR ketolide telithromycin (HMR-3647) may reach the market up to two years in advance of ABT-773

**Implications**

- The positioning that HMR adopts for their ketolide could impact the positioning of ABT-773. If the messages of Abbott and HMR are similar, it will be more difficult to create interest in ABT-773. Conversely, if the messages are vastly different, "believability" or confusion issues could exist.
- Any negative product characteristics of telithromycin could be perceived as "class" effects, thus impacting the perceptions of ABT-773.
- The extent to which HMR's ketolide is accepted on a given managed care formulary may initially limit ABT-773's acceptance until a subsequent formulary review is undertaken.
- Share gained by HMR represents share that ABT-773 may need to capture depending on relative positioning of the two products

**Strategies**

The strategy to address this issue consists of communication to the market as to advantages of ABT-773 over telithromycin (and other products). While this strategy will likely do little to reduce the uptake of telithromycin, it may facilitate the switching from telithromycin to ABT-773 once ABT-773 launches. Specific strategies include:

- Utilize competitive intelligence sources to obtain knowledge of product profile and positioning tactics
- Presentation of comparative information at scientific meetings, opinion leader advisories, and in journals
- Use of Abbott Medical Liaisons to disseminate information to key opinion leaders
- Work with PPD Managed Care to ensure that ABT-773 is well positioned within the managed care environment

**B. Opportunities****Opportunity #1**

Antimicrobial Resistance

**Implication**

Resistance is emerging as a key differentiating dimension in the antibiotic market. The differentiating potential of resistance can be further segmented along two dimensions: 1) ability of the agent to treat resistant pathogens 2) propensity for induced resistance with use of the agent. The extent to which ABT-773 performs along these two dimensions of resistance may translate into a competitive advantage over other agents.

**Objective**

Leverage the resistance profile of ABT-773 to gain competitive advantage

**Strategies**

- Gain an indication for drug-resistant Strep. pneumo, the most prevalent resistant respiratory pathogen. However, given that moxifloxacin will have this same indication (gatifloxacin and gemifloxacin may as well), this indication should be considered a required product characteristic rather than a source of competitive advantage.
- Conduct clinical and in-vitro comparisons between telithromycin, gemifloxacin, moxifloxacin, and gatifloxacin (among others) for drug resistant infections/organisms with the intent of showing comparable and/or superior efficacy to those agents.
- An Achilles' heel of the quinolones appears to be the relative ease with which pathogens (particularly Strep. pneumo) can develop resistance. Bacterial resistance to the quinolones, which was previously thought to occur only by means of gene mutation, was recently shown

to develop from a transferable plasmid, which may accelerate the rate of development of resistance to this class of antibiotics. Indeed, in-vitro data has shown it requires relatively few generations of a pathogen exposed to a quinolone before resistance is induced. Finally, it appears that the development of quinolone resistance may confer resistance to unrelated classes of antibiotics. An understanding of the mechanisms of quinolone resistance, the implications of that resistance to other antibiotic classes, surveillance data on the prevalence of mutations among strains of community pathogens, and related information should be obtained with the intent of using this information as part of a "counter-promotional" strategy. This could entail the building of awareness of such issues prior to launch via scientific meetings, advisories, etc. followed by true detailing efforts with this information upon launch.

### **Opportunity #2**

Potential for I.V. and oral suspension (pediatric) formulations

### **Implications**

While not currently funded, I.V. and oral suspension formulations represent an opportunity along several dimensions. Biacin is not available in I.V. and Biacin oral suspension has not been well accepted due to taste issues. Hence, these two formulations represent an opportunity for enhanced franchise visibility in two key channels, hospitals and pediatrics. An I.V. formulation can also result in greater access to hospital formularies and can pay dividends in greater tablet business stemming from I.V. step-down therapy. Beyond the incremental sales that an oral suspension formulation would provide, it also sends a strong signal to the market that the agent is safe. This will be an important part of the promotional strategy for competing with the quinolones, which have been unable to obtain pediatric indications because of various safety issues.

### **Objective**

Develop I.V. and oral suspension formulations

### **Strategies**

- Obtain funding for I.V. and oral suspension formulations for FY2000
- Develop the formulations in accordance with the product profiles shown in Section V

### **Opportunity #3**

Exploiting a new product class-ribosome binding

### **Implication**

The new ketolide class may result in a high interest level among the target market, including potentially greater access to managed care formularies.

### **Objective**

Leverage the "new class" status to increase market awareness and acceptance

**Strategies**

- Presentation of comparative information at scientific meetings, opinion leader advisories, and in journals
- Use of Abbott Medical Liaisons to disseminate information to key opinion leaders
- Establish ABT-773 web page and, nearing and during launch of telithromycin, direct Biacin sales reps to distribute the web address as part of the Biacin sales call (Medical Regulatory must be consulted).
- Work with PPD Managed Care to ensure that ABT-773 is well positioned within the managed care environment

## VIII. STRATEGIC MARKETING MIX

### PRODUCT:

#### A. USAN/Branding Strategy

- Identification of generic name in progress; estimated completion 12/99. Candidate names will be filed with USAN, with approval approximately 12 months post-submission.
- Brand name creation initiated 8/99 with Interbrand. Objective is to identify a single global brand that will be used in all markets. Identification of candidate names for submission to Patent and Trademark Office 1Q2000. Brand name will also be registered as the website for ABT-773.
- The intent will be to utilize the brand name as much as possible for communications external to Abbott, e.g. advisories, scientific meetings, press releases, etc.

#### B. Formulation Plan

- ABT-773 will be available in a tablet; the goal is to have a QD formulation, which appears likely based on phase IIa and pharmacokinetic studies. Multiple tablet strengths may be available, pending phase IIb studies and marketing research/positioning studies.
- Funding for I.V. and oral suspension (pediatric) formulations has not yet been achieved. It is likely that these programs will be funded for FY2000. Development plans for these two formulations are being established as of this writing.

#### C. Packaging

- Determine value of a convenience pack strategy in light of ultimate product positioning

### COMMUNICATION STRATEGY:

#### A. Professional

The focus of the communication strategy is toward professionals. Activities currently ongoing in this arena include opinion leader development through advisories and "VIP" visits, posters/presentations at scientific meetings, and articles in journals. An ABT-773 Communication Strategy Group consisting of NPD, AI New Product Planning, and Venture representatives meets monthly to plan communication activities.

#### B. Consumer

No activities planned.

**C. Associations/Agencies**

While no activities are currently ongoing, work to identify agencies/organizations whose policies are consistent with the positioning of ABT-773, specifically with regard to resistance and appropriate use, will be initiated. The CDC and WHO are potential partners, both of whom have issued statements regarding appropriate use of antibiotics.

**D. Managed Care**

Work with managed care to develop pre-launch communication plan

**PRICING STRATEGY:**

This will be determined in the product positioning marketing research



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ABT – 773

## Descriptive Memorandum

*May 2000*

Abbott Laboratories

June 5, 2000

Hancock – ABT-773

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**ABT-773***Opportunity Overview*

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase IIb trials. It is scheduled to begin in phase III clinical trials in Q4, 2000 and has an expected U.S. launch date of January 2003. Ex-U.S. launches are projected for 2003 and 2004 for Europe and Japan, respectively.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales. Worldwide sales, including tablet/capsule, oral suspension and intravenous (I.V.) forms, are projected to top \$1 billion by 2007.

*The US Market*

The overall antibiotic market in the U.S. reached \$8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were \$5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped \$2.1 and \$1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
<b>TOTAL TAB/CAP</b>	<b>\$5,715.4</b>	<b>100.0%</b>	<b>8.9%</b>	<b>221.5</b>	<b>100.0%</b>	<b>0.1%</b>

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*U.S. Market Projections*

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.
- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everninomycins, peptides, others).
- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

*The Ex-U.S. Market*

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. Tab/cap represents the largest segment, with sales of \$9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rx's) and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rx's (29 million Rx's) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales (\$370MM).

*Scientific Rationale for ABT-773*

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant gram + organisms, particularly macrolide resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

*Clinical Studies*

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Presumed Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
<i>S. pneumoniae</i>	100% (13/13)	90% (9/10)	96% (22/23)
<i>M. catarrhalis</i>	100% (6/6)	100% (7/7)	100% (13/13)
<i>H. influenzae</i>	96% (23/24)	92% (24/26)	92% (47/50)
<i>H. parainfluenzae</i>	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	6% (3/48)

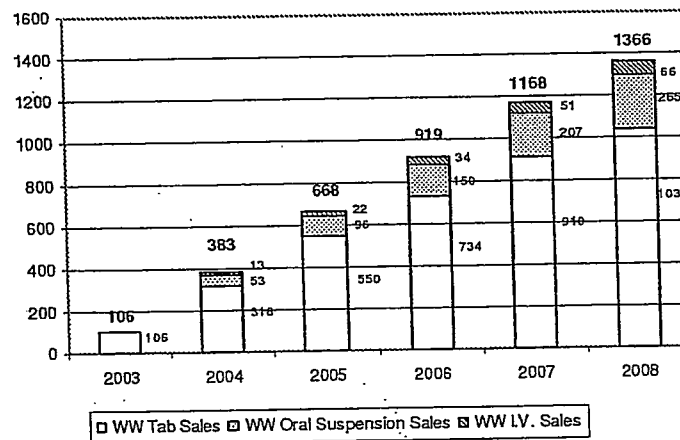
Clinical and Bacteriological Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

*Patent Status*

ABT-773 will have patent exclusivity through 2016.

*Financial Projections***Total Worldwide ABT-773 Net Sales (\$MM)****Total Worldwide ABT-773 Net Sales by Form (\$MM)**

	2003	2004	2005	2006	2007	2008
US Tablet Sales	64	159	289	383	481	570
US Oral Suspension Sales		41	59	88	123	162
US I.V. Sales		12	18	26	37	48
<b>Total U.S. Sales</b>	<b>64</b>	<b>212</b>	<b>366</b>	<b>497</b>	<b>641</b>	<b>780</b>
Ex-US Tablet Sales	43	157	261	352	430	465
Ex-US Oral Suspension Sales		12	38	63	84	103
Ex-US I.V. Sales		1	4	8	14	18
<b>Total Ex-US Sales</b>	<b>43</b>	<b>170</b>	<b>303</b>	<b>423</b>	<b>528</b>	<b>586</b>
<b>Total Worldwide ABT-773 Sales</b>	<b>106</b>	<b>383</b>	<b>668</b>	<b>919</b>	<b>1168</b>	<b>1366</b>

*Assumptions for Financial Projections*

- The tab form of ABT-773 launches in the U.S. and ex-U.S. in 2003; I.V. and oral suspension launch in 2004.
- 5 day QD compliance pak available.
- ABT-773 priced competitively with other macrolides, ketolides and quinolones in market at time of launch.
- Efficacy against multi-drug resistant Strep. pneumoniae is main point of differentiation vs. beta-lactam, macrolide and quinolone antibiotics.
- Tolerability equivalent to Zithromax.

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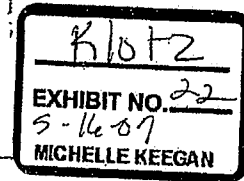
- Appendix 1

## Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

**PLs' HY**





**From:** Lynn C. Klotz [LynnKlotz@compuserve.com]  
**Sent:** Tuesday, July 04, 2000 12:30 PM  
**To:** Blewitt, Stephen  
**Subject:** ketolide research summary

Steve,

Here is the summary research on ketolide antibiotics. This might be the most promising of Abbott's single drugs in the package. It may even achieve the greater than \$1 billion market share they project, since Adventis publically projects \$1 billion for its ketolide, Ketek, just on the market. Abbott's is not far behind and may have superior properties.

I will complete the summary research writeups on the trip, and send them to you when I return shortly after July 10.

As far as a final report, I will make sure you have all the information verbally first. I am planning one page for each basket item which will summarize the most salient facts. The interviews and slightly polished research summaries will be in Appendices.

-Lynn

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### **Abbott's Ketolide Antibiotic (ABT-773)**

file: abbott-ketolide

#### Potential interviewee's for ABT-773

Stuart Levy (Professor Microbiology Tuft's University School of Medicine, Tel: 617-636-6764, e-mail: stuart.levy@tufts.edu) is a leading authority on antibiotic resistance. If he views ketolides as particularly promising we may not need to interview anyone else.

Malathum K, Coque TM, Singh KV, Murray BE  
(*Good interview candidates*)  
Center for the Study of Emerging and Re-Emerging Pathogens, University of Texas  
Medical School, Houston 77030, USA.

Schulin T, Wennersten CB, Moellering RC Jr, Eliopoulos GM  
Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard  
Medical School, Boston, MA 02115, USA.  
(*Excellent interview candidates, because of local connection. Does Andy Onderdonk know these researchers*)

Strigl S, Roblin PM, Reznik T, Hammerschlag MR  
Division of Infectious Diseases, Department of Pediatrics, State University of  
New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.  
(*Possible interview candidates*)

#### Questions for antibiotic resistance experts on ketolide antibiotics

What new classes of antibiotics show promise against resistant gram-positives?

Of the following new classes, which are the most promising: Quinolones, polyketides, macrolides, ketolides, others? Why?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

Which of the large drug companies do you see as leaders in the development of new antibiotics?

The antibiotic market is highly fragmented. In business terms, there are many antibiotics each with small market share. What would be the properties of a new antibiotic that would make it widely used? Of the development stage antibiotics, do you see one or more that should find wide usage, and thus large market share?

Are there any other approaches to protection against infections that will significantly compete

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with antibiotics? Vaccines? Vaccines in edible plants? Others?

Are there any other approaches to antibiotic resistance, besides new antibiotics, that seem promising?

Is there a key question that I did not ask? What is it, and how would you answer it?

Questions for Abbott on ABT-773 and competition

HMR 3647 is a Hoechst Marion Roussel antibiotic. It appears in more than one recent paper as especially promising. In view of the fact that Aventis is the name of the Hoechst/Rhone-Poulenc merger, is Ketek just the new name for HMR 3647?

Is ABT-773 also more effective against strains susceptible to other antibiotics?

What other new classes of antibiotics show promise against resistant gram-positives?

On average, what percentage of gram-positive infections are resistant to antibiotics? How fast is resistance growing?

In one literature report of a comparative test between Hoechst's ketolide (HMR 3647) and ABT-773, ABT-773 was found to be more active. Are there other ketolides for which you have comparisons?

How did you arrive at future sales of over \$1.3 billion?

Example articles

2: Antimicrob Agents Chemother 2000 Jun;44(6):1562-7

Studies of the novel ketolide ABT-773: transport, binding to ribosomes, and inhibition of protein synthesis in streptococcus pneumoniae.

Capobianco JO, Cao Z, Shortridge VD, Ma Z, Flamm RK, Zhong P  
Infectious Disease Research, Abbott Laboratories, Abbott Park, Illinois 60064,  
USA.

[Medline record in process]

Macrolide resistance in *Streptococcus pneumoniae* has been associated with two main mechanisms: target modification by Erm methyltransferases and efflux by macrolide pumps. The ketolide ABT-773, which has a 3-keto group and no L-cladinose sugar, represents a new class of drugs with in vitro activity against a variety of resistant bacteria. Several approaches were undertaken to understand how ABT-773 was able to defeat resistance mechanisms. We demonstrated tighter ribosome binding of ABT-773 than erythromycin. We also showed that ABT-773 (i) accumulated in macrolide-sensitive *S. pneumoniae* at a higher rate than erythromycin, (ii) was able to bind with methylated ribosomes, though at lower affinities than with wild-type ribosomes, and (iii) accumulated in *S. pneumoniae* strains with the

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efflux-resistant phenotype. (*Abbott has done research on the resistance mechanism.*)  
PMID: 10817709, UI: 20277881

3: Antimicrob Agents Chemother 2000 Apr;44(4):1112-3

In vitro activity of ABT 773, a new ketolide antibiotic, against *Chlamydia pneumoniae*.

Strigl S, Roblin PM, Reznik T, Hammerschlag MR

Division of Infectious Diseases, Department of Pediatrics, State University of

New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098, USA.

(Possible interview candidates)

The in vitro activities of ABT 773, telithromycin (HMR 3647), azithromycin, clarithromycin, erythromycin, and levofloxacin were tested against 20 strains of *Chlamydia pneumoniae*. (*Good, this is a comparative test between Hoechst's ketolide and Abbotts*) The MIC at which 90% of the isolates were inhibited and the minimal bactericidal concentration at which 90% of the isolates were killed by ABT 773 were 0.015 microg/ml (range, 0.008 to 0.015 microg/ml). ABT 773 was the most active antibiotic tested in this study. (*This is in vitro, what about comparative animal studies?*)

PMID: 10722526, UI: 20187185

4: Antimicrob Agents Chemother 2000 Feb;44(2):447-9

In vitro activity of ABT-773, a new ketolide, against recent clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Brueggemann AB, Doern GV, Huynh HK, Wingert EM, Rhomberg PR

Medical Microbiology Division, Department of Pathology, University of Iowa

College of Medicine, Iowa City, Iowa 52242, USA.

(Also a possible interview candidate)

The in vitro activity of ABT-773 was evaluated against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates. ABT-773 was the most active antimicrobial tested against *S. pneumoniae*. ABT-773 and azithromycin were equivalent in activity against *H. influenzae* and *M. catarrhalis* and more active than either clarithromycin or erythromycin. (*Again, good in vitro results for Abbott*)

PMID: 10639382, UI: 20107001

02831133 (THIS IS THE FULLTEXT)

Respiratory Tract Infections: Ketolides Comprise New Family of Antibiotics (Aventis' antibiotic Telithromycin shows in vitro activity against pathogens that lead to community-acquired respiratory tract infections; according to PROTEKT study) TB & Outbreaks Week, p N/A June 13, 2000

DOCUMENT TYPE: Newsletter (United States)

LANGUAGE: English RECORD TYPE: Fulltext

WORD COUNT: 641

ABSTRACT:

Preliminary data reported from PROTEKT (Prospective Resistant Organism Tracking for the Ketolide Telithromycin), a global study involving 66 laboratories, has found that telithromycin

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has demonstrated in vitro activity against pathogens that lead to community-acquired respiratory tract infections (RTIs) *(This study involves only the Aventis antibiotic, and is sponsored by Aventis)* Telithromycin is part of new family of antibiotics known as ketolides, being explored as RTIs grow increasingly resistant to commonly used antibiotics. Globally, RTIs kill more than 50 mil people yearly. PROTEKT is sponsored by Aventis Pharma. Ketek (telithromycin) was submitted by Aventis Pharmaceuticals to the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for marketing approval earlier in 2000. Full text further discusses the PROTEKT study.

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